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GASTRIC ACID AND GASTRIN PROFILES
IN HEALTH AND DISEASE

by

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Supervisor

DATE

Dedicated to my parents,

my past, present and future teachers

ABSTRACT

It is generally believed that gastric acid (H^+) is important in the pathogenesis of duodenal ulcer (DU). The role of H^+ in gastric ulcer (GU) and gastroesophageal reflux (GERD) is less well defined. However, one of the approaches to therapy of these conditions has been directed towards gastric acid suppression. Accordingly, a series of studies were conducted to evaluate the intragastric H^+ and serum gastrin profiles in 31 DU, 8 GU, 6 GERD and 7 normal subjects (N) over a 24-hour period under physiologic conditions closest to real life. Patients with DU tended to have higher basal acid output (BAO) than N but there was a considerable overlap. The values of BAO in GU and GERD patients overlapped with the values in N. In response to pentagastrin, the maximal acid output (MAO) was higher in DU than in GU or N. The mean MAO was similar in GERD and in N. The 24-hour pH profile was similar in all subject groups although the pH values remained > 4.0 for a longer period in GU than in DU or N. Furthermore, the H^+ activities after each meal, overnight and over 24-hour period were similar in all subject groups. The basal gastrin concentration (G) in GU was higher than that in DU whose value was higher than that in N. However, the differences in the basal G between these subject groups failed to reach significant levels. Neither was the difference in basal G between patients with GERD and normal subjects significant. The postprandial G responses were higher in DU, GU, GERD than that in N. Indeed, the G responses following meals were numerically higher in GU than in DU.

The antisecretory property of cimetidine 600 mg bid (C) was evaluated in 23 DU, 8 GU and 7 DU. C was associated with H^+ suppression

after breakfast, overnight and over 24-hour period in DU and N, whereas H^+ suppression was observed at all time periods in GU patients treated with C. This more prolonged H^+ suppression by C in GU than in DU or N cannot be explained by the difference in intragastric H^+ or in gastrin concentration. The ratio of H^+:G tended to be higher in N than in DU or GU. This H^+:G was markedly suppressed by C in DU and GU, but was minimally suppressed by C in N. This suggests that C may alter the sensitivity of parietal cells to endogenous gastrin in these DU and GU patients.

Cimetidine is commonly used in the treatment of acid pepsin disorders. For the purpose of improving patient compliance, the dosage of cimetidine was modified to 600 mg twice a day. This twice daily cimetidine was associated with lower H^+ after breakfast and overnight when compared to the conventional dose of cimetidine 300 mg qid. This superiority cannot be explained by the change in gastrin concentration or by the difference in serum cimetidine concentration as similar postprandial gastrin responses and cimetidine pharmacokinetics were observed in the two cimetidine regimens.

Some patients with acid-pepsin disorders fail to respond to a single agent therapy. This failure of response may be related to inadequate acid suppression. The antisecretory effect of combination therapy of cimetidine with antacid or with an antimuscarinic agent was tested against a single agent. This study showed that both Mylanta II and pirenzepine potentiate and prolong the acid suppressing effect of cimetidine. The study also suggested the superiority of ranitidine over cimetidine in H^+ suppression in patients with GERD. Enprostil (E), a synthetic dehydro-prostaglandin E_2 given as 35 mcg bid is a potent antisecretory and antigastrin agent. The nocturnal H^+ was similarly suppressed by E 35 mcg bid and by E 70 mcg hs.

This study suggests the similarity of 24-hour intragastric H^+ profile in patients with acid-pepsin disorders and normal subjects. Patients with DU and GU differ from normal subjects in their BAO, MAO and in their food-stimulated gastrin responses. We speculate that acid may only play a permissive role in the pathogenesis of the diseases. Gastric acidity can be suppressed by the administration of cimetidine in all subject groups. Greater acid suppression can be achieved simply by modifying the dosage regimen or by using combination therapy. The studies provide some basis for the selection of therapeutic regimens in the treatment of acid-pepsin disorders. The potent antisecretory regimens would certainly benefit those who are acid hypersecretors. On the contrary, other modes of therapy may be more beneficial in the other subgroups of patients whose factors other than gastric acid secretion are impaired.

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1. INTRODUCTION

1.1 General

Peptic ulcer is believed to occur when there is an imbalance between the aggressive factor of acid and pepsin, and the defensive factor of mucosal resistance (60). It is manifested by an interruption of the gastroduodenal mucosa extending through the muscularis mucosae. The pathophysiological and therapeutic approaches so far have been mainly focused on the aggressor side of gastric acid and pepsin. On the one hand, gastric and duodenal ulcers are usually grouped together as peptic ulcer disease which signifies the role of acid and pepsin in the formation of ulcer. On the other hand, there is genetic, environmental and pathophysiologic evidence suggesting that they are of different disease entities.

Different physiological abnormalities have been described in patients with gastric ulcer and duodenal ulcer. The role of gastric acid in the pathogenesis of duodenal ulcer is demonstrated by the therapeutic efficacy of the antisecretory agents in the treatment of duodenal ulcer. Some patients with duodenal ulcer have high basal and stimulated acid output, although there is often an overlap with normal subjects (44). However, duodenal ulcer has never been reported in patients with achlorhydria. On the other hand, duodenal ulceration is common in patients with hypersecretory states such as in Zollinger-Ellison syndrome.

The importance of gastric acid in gastric ulcer is less well defined. The acid secretory capacity in patients with gastric ulcer may depend on the anatomical location of the ulcer or its association with duodenal ulcer. Gastric ulcer may be classified into three main types according to the location of the ulcer and the acid secretory capacity: type I consists of ulcer in the body of the stomach and represents 57% of all gastric ulcers which are hypersecretors; type II is the group whose ulcer in the body of the stomach is combined with duodenal ulcer and comprises 22% of total patients with gastric ulcer who also are hypersecretors; the other 20% is the type III prepyloric ulcer who have acid hypersecretion and behave like duodenal ulcer (48). Although the majority of gastric ulcer patients secrete lower amounts of acid than does the normal population, the role of acid in the formation of gastric ulcer cannot be totally excluded. Achlorhydria may only be the consequence of established ulceration. It has been postulated that the loss of luminal hydrogen ion (H^+) may occur with increased H^+ back diffusion through the damaged mucosa. The concomitant inflammation may lead to impaired secretory capacity and the refluxed duodenal content may neutralize the gastric acidity. Some recent studies have shown that antisecretory agents are effective in the healing of gastric ulcer (30).

Gastroesophageal reflux disease is another acid-pepsin disorder in which gastric acid may be important in the pathogenesis of the disease (33,39). Altered gastric acid secretion has not been well described in gastroesophageal reflux disease although refluxed gastric acid may increase the propensity for mucosal damage. One of the mainstays of the treatment of reflux esophagitis is a reduction in gastric acid.

In spite of the accepted role of acid in peptic ulcer disease, it is still not clear how much acid is required for the formation of the ulcer and how much acid is needed to be suppressed to attain the healing of the ulcer. Not all patients with ulcer necessarily secrete higher than normal amounts of gastric acid. In this instance, the other side of the balance which predisposes to ulcer formation might become more relevant.

A pathophysiologic role of altered gastrin metabolism in peptic ulcer disease has been postulated. The increased gastrin release after food or sham feeding has been reported in duodenal ulcer (63), and elevated gastrin concentration was reported in gastric ulcer (21). Fasting gastrin concentration has previously been shown to be elevated in patients with gastroesphageal reflux disease (84).

1.2 Aims and Scope of Research

Therapy of peptic ulcer disease so far has been directed towards the reduction of gastric acid. The use of antisecretory agents that have been introduced are based on the knowledge of parietal cell function. Failure to respond to antisecretory agents has been reported and this may be related to inadequate acid suppression or may be due to the fact that factors other than acid are responsible for ulcer formation. A series of studies have been undertaken directing towards a better understanding of the role of acid and gastrin metabolism in peptic ulcer disease. The objectives were:

1. To develop a technique for assessing gastric acid profile and gastrin response to a meal under physiologic conditions in normal volunteers and in patients with peptic ulcer disease.

2. To evaluate the pharmacological effects of various antisecretory agents in normal volunteers and patients with peptic ulcer disease. From the practical standpoint, the most effective acid suppression regimen either, by dosage modification or by combining

therapy, can be determined. This may be necessary in patients who fail to respond to conventional therapy or in patients with an acid hypersecretory state.

3. To determine the effect of these antisecretory agents on serum gastrin concentration.

4. To develop a model for studying pharmacokinetics of antisecretory agents and drug interaction when combination therapy is used.

5. To determine the relationship between gastric acidity and gastrin response in patients with peptic ulcer disease and normal subjects.

2. LITERATURE REVIEW

2.1. Anatomical Background

Structure of Gastric Mucosa

The gastric mucosa is lined by a simple columnar epithelium with numerous tubular invaginations called the gastric pits (45). Single or multiple tubular gastric glands, either simple or branched, open into the base of the gastric pits. The lamina propria which is a loose connective tissue underneath the gastric epithelium contains blood vessels, nerves, smooth muscle cells and various connective tissue cells. The muscularis mucosa is the muscle layer that separates the gastric mucosa from the submucosa. The submucosa is a layer of dense connective tissue which contains blood vessels and nerves, including the Meissner's plexus. The lymphatic plexuses are dispersed in the muscularis mucosa and submucosa and projected into the lamina propria. The muscular coat of the stomach consists of smooth muscle cells arranged as oblique, circular and longitudinal layers. In between these muscular layers, is the Auerbach's plexus, which is a sympathetic nerve plexus. The serosa is the outermost layer which is a thin layer of loose connective tissue covered by a layer of squamous cells (46).

There are three main types of gastric glands: the cardiac, pyloric, and oxyntic (or fundic) glands. The cardiac glands occupy the area adjacent to the esophagus. The predominant cells are mucous cells which produce secretion rich in mucus. They also contain undifferentiated and endocrine cells. The oxyntic glands occupy most of the fundus and body of the stomach. They contain oxyntic parietal cells which secrete hydrochloric acid, chief cells which secrete pepsinogen, mucous neck cells, undifferentiated cells and endocrine cells. Chief cells are the major cell type in the base of the gland; parietal cells predominate in the isthmus and neck regions, intermingled with mucous neck cells, undifferentiated cells, and a few chief cells. The endocrine cells are located between the other cell types. The pyloric gland area is located in the gastric antrum adjacent to the oxyntic gland area in the body of the stomach (57). The pyloric glands contain mucous secreting cells and G-cells which are the major source of gastrin.

Ultrastructure of the Parietal Cell and their Morphological Transformation

Parietal cells contain large numbers of mitochondria which account for about 30% of the cell volume indicating an important contribution of oxidation metabolism to the energy supply of the cell (41). The cell contains an infolding of the apical membrane called intracellular canaliculus (47). In the resting state, the cytoplasm of the parietal cell is filled with tubulovesicles which are specialized smooth endoplasmic reticulum. With stimulation of secretion, it was shown that these tubulovesicles fuse with the apical membrane forming extensive secretory canaliculi with numerous microvilli and communicate with the luminal surface of the cell. Removal of the stimulus reverses the ultrastructure back to its resting state (29).

2.1. Gastric Acid Secretion

The gastric hydrochloric acid (HCl) content approximates 160 mM, which is isotonic to plasma. This hydrochloric acid is secreted by the parietal cells. The role of parietal cells in gastric acid secretion is based on indirect evidence using animal experiments. Several experimental models have been used for the study of acid secretion by the gastric mucosa. Physiological and morphological changes in response to acid stimulation can be assessed in intact gastric mucosa, isolated parietal cells, isolated gastric glands and membrane vesicles (80). It has been generally accepted that the site of acid secretion is the secretory canaliculus of the parietal cell (41). Direct measurement of acid secretion is generally not useful to assess the response to stimulation, since the response is transient and is neutralized by bicarbonate secretion. Several other indirect indices of parietal cell responses to stimulation have been developed. As the secretion of gastric acid is a highly energy dependent process, the rate of oxygen consumption is increased with stimulation, and this can be measured by using polarographic electrodes or respirometers (90). Morphological transformation of the parietal cell can be assessed during stimulation of acid secretion. Lastly, the accumulation of a weak base in the acid compartments can be assessed to study the response of parietal cells to stimulation (12).

Accumulation of a weak base in the low pH compartment has been used to assess acid secretion. Aminopyrine is a weak base used to assess parietal cell function in secreting acid. With its pKa of 5.0, it remains mostly in the unionized form which is freely permeable to biological membranes at physiological pH. Aminopyrine becomes ionized at acidic pH; for example at a pH near 2.0, the ionized form of aminopyrine increases several thousand-fold. This unionized form is poorly permeable across lipophilic barriers. Accumulation of aminopyrine in the acid space, with a pH gradient across a lipophilic barrier, is therefore used as an index to monitor acid secretion by parietal cells (11,12). It does not necessarily provide a direct index of the rate of acid secretion, but rather is a measure of the concentration of sequestered acid in a specific space.

An oxidation-reduction mechanism (42) and ATP (10) have been proposed as energy sources for acid secretion. According to the redox scheme, H^+ is generated from the oxidation-reduction process and is delivered to the secretory surface via the electron transport system (Figure 1).

A protein donor, AH_2, is oxidized by a membrane bound redox system so that H^+ is transported across the membrane. The electrons are transferred to an acceptor located on the cytoplasmic surface. The proton is delivered to the secreted fluid and the electron is delivered to the respiratory chain, and eventually is delivered to oxygen. A hydroxyl ion (OH^-), generated for every proton released, reacts with CO_2 coming from intracellular metabolism or from blood to form bicarbonate (HCO_3^-). The reaction between CO_2 and OH^- is catalyzed by enzyme carbonic anhydrase.

ATP is another proposed source of energy for acid secretion. K^+ dependent ATPase was identified in microsomal membranes derived from fundic mucosa (31,85). This enzyme has been localized by the immunochemical method in the secretory canaliculi of the parietal cells (77). The appearance of ATPase is associated with the onset of acid secretion. Several other metabolic pathways including glycolysis, glucose oxidation and lipolysis have been proposed as additional sources of energy for parietal cells (78).

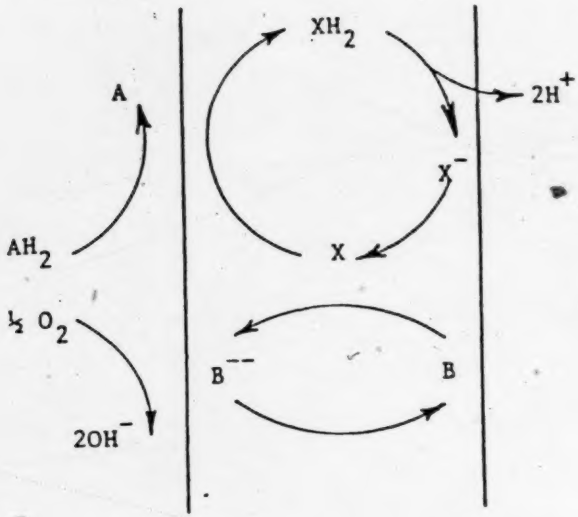
XH$_2$
A
2H$^+$
X$^-$
AH$_2$
X
½ O$_2$
B^{--}
B
2OH$^-$

FIGURE 1. Illustration of a redox scheme for gastric acid secretion (adapted from Reference 80).

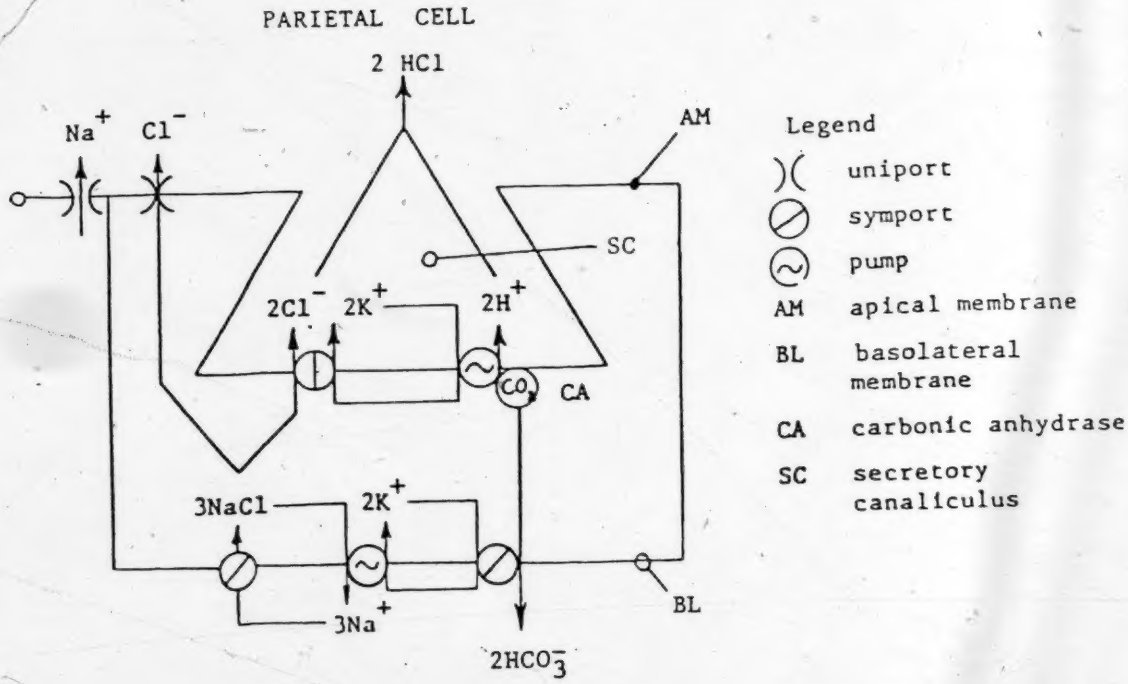
PARIETAL CELL
2 HCl
Na$^+$
Cl$^-$
AM
SC
2Cl$^-$
2K$^+$
2H$^+$
CO$_2$
CA
3NaCl
2K$^+$
3Na$^+$
BL
2HCO$_3^-$
Legend
)(uniport
⊘ symport
(~) pump
AM apical membrane
BL basolateral membrane
CA carbonic anhydrase
SC secretory canaliculus

FIGURE 2. A model of an ion transport in parietal cell for gastric acid secretion (adapted from Reference 79).

H^+ secretion occurs down an electrical gradient, but against a huge concentration gradient. Therefore, there must be an active pump independent of the luminal solution localized at the apical membrane of parietal cells. H^+ is actively secreted into secretory canaliculi in exchange for K^+, being catalyzed by H^+-K^+ATPase. At the basolateral membrane, there is an active Na^+-K^+ exchange operated by Na^+-K^+ATPase (Figure B). Na^+ recycles the cell through the NaCl symporter resulting in the accumulation of Cl^- in the cytoplasm. This Cl^- effluxes from the cell by two pathways: either through a uniport pathway present at the apical membrane, accompanied by Na^+ passing through paracellular pathway or by entering lumen of the secretory canaliculus in association with K^+. This K^+ at the luminal surface is necessary for H^+ exchange for HCl secretion (Figure 2).

The active transport of Cl^- into the lumen creates a negative potential of -40 to -70 millivolts. Most of the K^+ that had been secreted along with the Cl^- is reabsorbed, and H^+ take their place in the canaliculi. CO_2 either from intercellular metabolism or entering from the blood, combines with water under the influence of carbonic anhydrase to form carbonic acid. HCO_3^- produced from further dissociation of carbonic acid diffuses out of the cell at the basolateral membrane. There is an electrochemical gradient favoring net movement of Na^+ into the lumen. Nevertheless, the net output of Na^+ into the lumen is very small. The unidirectional flux of Na^+ from lumen to blood is about one fifth of the net output. The H^+ and Cl^- pumps are closely related. The tendency of the Cl^- pump to make the mucosal surface negative is opposed by the tendency of the proton pump to make it positive (28).

2.3 Control of Gastric Acid Secretion

Gastric acid secretion is regulated by three endogenous substances including acetylcholine, gastrin and histamine. These are delivered to the parietal cells via neurocrine, endocrine and paracrine pathways. The role of these endogenous substances in stimulating parietal cells to secrete acid have been studied using indirect indices of acid secretion: i.e. oxygen consumption, morphological transformation, and accumulation of aminopyrine (87). Studies using specific pharmacological antagonists confirm the role of these substances in gastric acid secretion.

Acetylcholine is released from the post-ganglionic vagal fibers to the parietal cells via muscarinic receptors. Gastrin is released by the antral G cell, stimulated by the direct effect of food nutrient in the gastric lumen (22). Gastrin is also released in response to vagal stimuli (67) and antral distention (82). Histamine is released from its storage sites either in the mast cells or in enterochromaffin cells in the gastric mucosa (87). The histamine then diffuses across the intercellular space to its target, the parietal cells.

Parietal Cell Receptors

With isolated parietal cells, the specificity of the receptors have been identified (80). There are two hypotheses that attempt to explain the actions of the stimulants of acid secretion by the parietal cells. The first model suggests that histamine is the final common mediator regulating the parietal cell function (15), with acetylcholine and gastrin activating the release of histamine from its store in the gastric mucosa. This concept would explain the ability of H_2 receptor antagonists to inhibit the action of acetylcholine and gastrin. But this would not explain the potentiating interactions of these secretagogues demonstrated in vivo, or the ability of anticholinergic agents to inhibit the action of histamine. The second theory suggests that the parietal cell has specific receptors for histamine, gastrin and acetylcholine (87). Histamine was shown to stimulate parietal cell function as evidenced by increased oxygen consumption, aminopyrine accumulation and morphological transformation of the cell (12). H_2 receptor antagonists inhibit histamine-stimulated gastric acid secretion, with a progressive parallel shift of the dose response with increasing dose of antagonist (88). Cholinergic agents have been shown to stimulate parietal cell function as evidenced by increased oxygen consumption, aminopyrine accumulation and morphologic transformation in the parietal cells with varying potencies depending on animal species (12). Gastrin was shown to produce a small but definite increase in both oxygen consumption and aminopyrine accumulation in the isolated parietal cells (88,91).

Potentiating interactions occur when the response to a combination of agents is greater than the sum of the individual responses. Potentiation between histamine and cholinergic agent, and histamine and gastrin were demonstrated (9,92). Although there is no direct potentiation between cholinergic agents and gastrin, potentiation between the two occurs when histamine is present (91,92).

Atropine inhibits not only vagal cholinergic stimulation of acid secretion, but also secretion stimulated by histamine or gastrin (53). Similarly, the histamine H_2 receptor blocker inhibits not only histamine stimulated secretion but also that elicited by gastrin or cholinergic stimulation (87). Interdependence of vagal activity and gastrin has been suggested by Olbe, who found that acid secretion decreased in response to vagal activation in dogs with antrectomy; the response could be restored with the administration of gastrin (68). In contrast, this finding was not found in man (51), suggesting that the interdependence of secretogogues may be species specific.

The action of histamine on the parietal cell is closely related to c-AMP production, as histamine stimulation of c-AMP production seems to correlate with parietal cell function (93,111). Also H_2-receptor antagonists have been shown to inhibit stimulation of c-AMP production in several animal studies (18,94). Further, analogs of c-AMP have been shown to stimulate parietal cell function (93). The inhibition of the c-AMP degrading enzyme phosphodiesterase was shown to potentiate the stimulatory action of histamine on parietal cells (93). Prostaglandins have been shown to inhibit acid secretion, and yet stimulate c-AMP production in intact mucosa (20). However, prostaglandin stimulation of c-AMP production has been found to be inversely correlated with the content of parietal cells in the cell separation technique (111). This suggests that cells, other than the parietal cells, are also responsible for the c-AMP production. Prostaglandins were shown to exert an inhibitory effect on the histamine action on parietal cells but not on cholinomimetic, gastrin or c-AMP analog (89). This suggests that prostaglandins specifically inhibit the action of histamine by blocking c-AMP production.

Cholinergic stimulation of gastric acid secretion is thought to be related to the flux of calcium into the parietal cell. The calcium channel blocker, lanthanum, was shown to impair cholinergic stimulation, and this can be restored by readdition of extracellular calcium. The cholinergic stimulation has been shown to be impaired with decreasing concentrations of extracellular calcium (86). Calmodulin, a calcium binding protein, increases with the influx of calcium (17). This protein was initially discovered as an activator of phosphodiesterase. Its calcium loaded forms also regulate the activity of several enzymes, including adenylate cyclase and phosphodiesterase. Calmodulin may play a role in the interaction of an intracellular messenger, regulating the breakdown of c-AMP and prostaglandin synthesis. The role of this calcium binding protein in the control of acid secretion needs to be further studied. The intracellular mechanism involved in gastrin stimulation of parietal cells is not yet known.

2.4 Gastric Secretory Response to a Meal

Constituents of Gastric Secretion

The principle components of gastric juice are water, hydrochloric acid, electrolytes, pepsin, intrinsic factor and mucus. Gastric contents also contain swallowed saliva and refluxed duodenal secretions. Both acid and pepsin increase in response to a meal but mucus secretion does not appear to be under the influence of feeding. The gastric secretory response to a meal is characterized by acceleration followed by deceleration. Based on the assumption that stimulatory and inhibitory forces are operated during both phases, the initial acceleratory phase would correspond to a predominance of stimulatory over inhibitory forces, whereas the converse would occur in the deceleration phase.

After a meal, acid secretion increases and is near the maximum that can be achieved with exogenous stimulant by 90 minutes. Inspite of this, the pH within the stomach remains relatively high, particularly during the first hour due to the buffering effect of food. Postprandial gastric secretory responses can be divided into three phases: predominantly stimulatory phase, predominantly inhibitory phase and intestinal phase.

Stimulatory mechanisms predominate during the first 30 to 60 minutes after a meal. Cephalic stimulation is important during this initial stimulatory phase. However, it was shown that the cephalic stimulation by modified sham feeding only provided about one-third of maximal secretory capacity (75). This cephalic phase is believed to be mediated by vagal stimulation of the parietal cells and partly through vagal stimulation of gastrin release (96). The effect of gastric distention on gastric acid secretion was shown to amount to one-third of the maximal secretory response. It is believed that fundic distention stimulates gastric acid secretion through vagovagal and intramural cholinergic reflexes (37), whereas antral distention decreases gastric acid secretion (83). Both stimulatory and inhibitory effects of fundic and antral distention probably operate simultaneously. Gastrin is released from the antrum under the effect of intraluminal nutrients such as amino acids and calcium. This component may account for the remaining acid response to a meal. The less well defined intestinal phase of postprandial gastric secretion may cause net stimulation or net inhibition of gastric acid secretion.

After the first postprandial hour, the gastric secretory rate declines due to weakening stimulatory forces and rising inhibitory forces. The effects of cephalic stimulation fade away and gastric distention diminishes as the volume of gastric contents begins to decline. The remaining stimulatory forces are the chemical action of food nutrients and the stimulatory force from the intestinal phase. Inhibitory forces become predominant in the last postprandial hour. Immediately after the ingestion of food, the intragastric pH rises due to the diluting and buffering effects of food. Intragastric pH gradually declines during the stimulatory phase of acid secretion, until a pH of about 2.0, which is optimal for peptic activity, is achieved. Acidification of gastric contents exerts a negative feedback control on gastric acid secretion. However, a decrease in secretion was observed even if gastric contents are artificially sustained at pH 5.5 by intragastric titration with alkali (27). This suggests that factors other than gastric acidification are responsible for the inhibitory effects. It was shown that duodenal acidification, by direct infusion of acid, could inhibit gastric acid secretion stimulated by either exogenous secretagogues or by gastric distention (50,112). Gastric and duodenal acidification may inhibit postprandial gastric secretion through neurohormonal mechanisms. Somatostatin, which inhibits acid secretion, may be released in response to low antral pH (104). Glucagon, similar to secretin, inhibits gastric acid secretion, but its physiologic role in regulating acid secretory response is not precisely known (59). When food enters the small intestine, both stimulatory and inhibitory actions occur during the intestinal phase. The net effect depends on the nutrient composition of chyme, the level of exposed intestine, and the period after a meal. Luminal protein stimulates gastric acid secretion when infused intraduodenally, but no effect was shown when this protein was infused intrajejunally (34). This acid secretion produced by intraluminal protein has been postulated to be mediated by the release of gastrin and enteroxyntin (36). Both luminal fat and carbohydrate have been shown to inhibit acid secretion at all levels in the intestine (69). An intestinal stimulatory action may have a more obvious effect later after meals when the gastric stimulatory force is declining.

Gastric emptying is also important in regulating the time over which this gastric stimulation of acid secretion takes place. Nutrients are emptied from the stomach at different rates depending on chyme composition, consistency and amount. Each of these factors also affects gastric secretory responses differently. For example: amino acids stimulate acid secretion whereas fat and carbohydrate inhibit acid secretion. The larger nutrient loads entering the jejunum have more pronounced effects on gastric response to the meal than the smaller nutrient loads.

Besides chemical properties, the physical characteristics of meals also influence the magnitude and duration of the gastric secretory responses. The cephalic phase would be influenced by the external appearance of a meal and by individual preferences. The route of ingestion also influences the gastric secretory response, as chewing during oral ingestion contributes to the cephalic phase of acid secretion (75). Swallowed saliva may affect both intragastric volume and acidity as it neutralizes some of the secreted acid. It is also possible that saliva contains substances which influence acid secretion.

It was shown that ordinary meals eaten in solid-liquid form resulted in a greater secretory response than identical meals delivered intragastrically after homogenization (61).

2.5 Methods of Gastric Acid Measurement

Several methods have been used for measuring gastric acid.

Gastric Aspiration

Gastric content is aspirated through a nasogastric tube which is placed in the most dependent part of the stomach under fluoroscopic x-ray control. The acidity of aspirated gastric juice can be determined by pH measurement using a glass electrode or by titration with sodium hydroxide (NaOH). The number of millimoles of NaOH needed to titrate the gastric juice represents the "titratable" acidity in millimoles per liter. The pH measured by the glass electrode is converted to hydrogen ion (H^+) using the standard table of Moore and Scarlata (66). This H^+ activity can be converted to H^+ concentration using activity coefficients previously published by these workers. It was pointed by Pounder et al that these activity coefficients do not apply to gastric juice containing food buffer (73).

This method cannot accurately measure acid secretion in the presence of food in the stomach. Secreted acid may be emptied from the stomach, neutralized by refluxed duodenal and pancreatic contents, saliva or non-parietal cell secretion, or may diffuse back across the gastric mucosa.

The basal acid output (BAO) can be measured by gastric aspiration in the absence of intentional or avoidable stimulation. The gastric juice is continuously aspirated and collected at 15-minute intervals over a one hour period. The volume and pH of the gastric contents are measured and the total acid output can be calculated from the products of the acid volume and concentration.

The acid secretory responses to secretagogues are expressed as maximal acid output (MAO) or peak acid output (PAO). The acid output is determined from the 15-minute fractions of gastric aspiration over a one hour period after the administration of pentagastrin (6.0 mcg/kg, subcutaneously) or histamine (40mcg/kg). The MAO (mmol/hr) is calculated by multiplying the highest value of acid output by four, and the PAO (mmol/hr) is calculated by multiplying the sum of two consecutive highest values of acid output by two.

The rate of BAO varies with time, whereas the PAO remains relataively constant over long periods of time. There is no correlation between BAO and serum gastrin concentration (32,102). However a correlation between BAO and serum pancreatic polypeptide, which is believed to be under vagal control, has been previously shown (64). PAO is a function of the subject's sex, body weight, lean body mass and weight. The MAO is thought to correlate with the number of parietal cells.

In vivo intragastric titration

This technique was introduced by Fordtran and Walsh (27). To measure acid secretion in the presence of food in the stomach, the intragastric pH is maintained at the pH of the homogenized meal (pH 5.5) by infusing 0.3N sodium bicarbonate ($NaHCO_3$). The number of milliequivalents of bicarbonate necessary to maintain gastric pH at 5.5 is assumed to be equal to the number of milliequivalents of acid secretion. The gastric samples are obtained every 2-3 minutes for the pH measurement. A previous study (25) suggested there were higher values for acid secretion with in vivo intragastric titration at pH 5 than with gastric aspiration. It was postulated that secreted acid may be incompletely recovered during aspiration. Acid secretion may be higher at pH 5 than when the pH is more acidic. In spite of the correction of transpyloric losses, using the nonabsorbable marker polyethylene glycol, with gastric aspiration (62) or changing the pH endpoint of intragastric titration to pH 2.5, the difference in acid secretion persists. Finally, gastric distention may contribute to increased acid secretion observed with the intragastric titration technique.

Intragastric pH monitoring has been a useful technique to assess the effects of diets and medications over a relatively prolonged period and under physiologic conditions closest to real life. This acid milieu, determined by pH measurement, represents the actual condition where medications are to be used. The concentration or activity of gastric acid in the stomach may be more important than the actual amount of secreted acid in providing the H^+ available for damage at the mucosal membrane. It is presumed that the gastric content is well-mixed considering the peristaltic activity of the stomach and correlation between intragastric acidity and intraduodenal acidity was previously shown (3). It is not known whether the acid volume, acid concentration or total acid output is the major determinant of mucosal injury. The gastric volume may be important as it would determine the total acid load into the duodenum or the total amount of acid remaining in the stomach, which might predispose to ulcer formation or reflux into the esophagus. On the other hand, the acid concentration present at the mucosal membrane, regardless of the volume, may increase propensity to mucosal damage. Comparative effects of different antisecretory regimens on gastric pH and gastrin profiles are the main interests in interpreting the results.

The pH profile is influenced by the quantity and nature of food (5,14). It is therefore necessary to control the diet and the timing of samples when an effect of antisecretory drug is tested.

2.6 Gastrin Metabolism

Chemistry

Gastrin is a chain of amino acids with N-terminal on one end and carboxy-terminal on the other end. There are multiple molecular forms of gastrin and they are abbreviated according to the number of amino acid residues that they contain. They occur either in sulfated or nonsulfated form. The most abundant forms of human gastrin are G-34 and G-17. A larger molecular form of gastrin, G-34, or big gastrin, was identified in plasma and tissue by Yalow and Berson (114). Gastrin heptadecapeptides or G-17, were purified from human antral mucosa by Bentley et al (8).

Most of stored hormone in the G-cell is the G-17 form. It is believed that conversion of G-34 to G-17 takes place in the G-cell. The other molecular forms identified are big-big gastrin (115), which has not been characterized chemically and biologically, and the smaller form of G-14. The biological actions of the gastrin molecule are determined by the carboxy-terminal portion. Molar potency has been shown to increase with chain length from G-14 to G-34, when expressed as the exogenous dose required to achieve maximal response (107). When considering blood levels needed to achieve maximal responses, G-17 was shown to be more potent on a molar basis than G-34 (107). However, the blood level is determined by the clearance rate of the hormone. Recently, it was shown that synthetic G-34 is as potent as G-17 on a molar basis in normal control and duodenal ulcer subjects (23).

Pentagastrin is a gastrin-like peptide, a commerically available synthetic pentapeptide consisting of the C-terminal tetrapeptide amide of gastrin. Its potency is comparable to that of the C-terminal pentapeptide amide of gastrin. The C-terminal pentapeptide amide sequence of gastrin and cholecystokinin (CCK) is identical, and this fragment has all the biologic actions of both hormones.

Distribution of Gastrin

By using immunocytochemical studies, it was shown that gastrin-containing G-cells are located in the gastric antrum and in the proximal duodenum (35). G-cells have a flask shape with a broad base and a narrow neck that extends to the mucosal surface. Gastrin-containing storage granules are at the base of the cell and microvilli are present at mucosal surface. These microvilli may contain receptors for stimulation and inhibition of the G-cells by intragastric contents.

G-17 is the major gastrin in the extract of antral mucosa. The highest concentrations of intestinal gastrin are found in the proximal duodenum, with progressively lower concentrations in the remainder of the duodenum and jejunum. After antrectomy and gastroduodenostomy, the increase in serum gastrin in response to feeding was shown to be as great as before antrectomy (97). In the basal state, about two-thirds of the serum gastrin is G-34. G-34 and G-17 increase following food, with about half of the serum gastrin being G-34 postprandially.

Measurement

Radioimmunoassays have been developed for the measurement of serum gastrin with high sensitivity and specificity (65,76). The most common and versatile gastrin radioimmunoassay utilizes antibodies specific for the biologically active C-terminus of gastrin that react approximately equally well with G-34, G-17 and G-14, and exhibit minimal cross reactivity with CCK peptides. G-34 is the predominant circulating form and G-17 comprises 10-30 percent of total immunocreativity. Very small amounts of G-14 may be present in the serum. Because of the heterogeneity of circulating gastrin and because different molecular forms vary in biologic activity, total gastrin activity determined by radioimmunoassay only represents a crude index of bioactivity.

Regulation of Gastrin Release

The release of gastrin from the G-cells is under the influence of chemical mediators. Under physiologic conditions, gastrin release is stimulated by intraluminal peptides, amino acids, gastric distention, and vagal cholinergic activation. The physiologic roles of calcium and epinephrine on their stimulating effects of gastrin release are not known (55,56).

The role of cholinergic mechanisms for gastrin release in man has not been established. Sham feeding causes release of gastrin (52), but carbachol infusion failed to increase serum gastrin concentration. Atropine enhances rather than inhibits gastrin release in response to vagal stimulation (24). This implies that cholinergic control of gastrin release is both stimulatory and inhibitory. The role of gastric distention on gastrin release in man has not yet been proven, although gastrin was shown to be released when antral or fundic portion of the stomach were distended in the dog.

The release of gastrin is under negative feedback control, in which gastric acid secreted in response to gastrin inhibits further release of gastrin. Gastrin release in response to stimulants is under the influence of intraluminal pH. However, the acid and alkali have little or no effect on unstimulated resting gastrin levels. Secretin, glucagon, VIP, and GIP inhibit the release of gastrin from G-cells, and also inhibit the action of gastrin on parietal cells (106).

Metabolism

In dogs, the half-lives of G-17, G-34, and big-big gastrin are found to be approximately 3, 9 and 90 minutes respectively (98). The half-life of G-14 is about the same as G-17. The half-lives of natural human G-17 and G-34 were found to be 5 and 42 minutes respectively (108).

Gastrin is excreted through the kidney and is presumably metabolized within the kidney, as very little gastrin appears in urine. An increased serum gastrin concentration occurs in nephrectomized patients and patients with severe renal disease (54).

The small intestine also appears to play a role in gastrin metabolism. Hypergastrinemic responses to feeding have been shown in patients following a massive intestinal resection (99). It has been suggested that the liver plays a minor part in the inactivition of G-17. The liver actively removes shorter, biologically active gastrin fragments from the portal circulation, including the tetrapeptide and pentagastrin.

The basal gastrin concentration in duodenal patients has been shown to be similar to the values observed in control subjects (103). It is not known what proportion of this basal gastrin is composed of biologically active forms of the hormone. However, there is no correlation between the basal acid output and the basal gastrin concentration in patients with either duodenal ulcer or gastric ulcer (110). The gastrin concentration in response to feeding has been shown to be higher in both duodenal and gastric ulcer patients (21,63) than in normal subjects. It was shown that G-34 responses to feeding were higher in duodenal ulcer and gastric ulcer subjects than normal, but G-17 responses were similar (100). Further, the G-34 responses to feeding were shown to be higher in gastric ulcer than in duodenal ulcer patients (16). There is no difference in the proportion of G-34 or G-17 in antral or duodenal tissue in patients with gastric or duodenal ulcer (16). Duodenal ulcer patients have been shown to have increased sensitivity to exogenous pentagastrin (44) and their feedback mechanism of gastrin release may be defective (109).

2.7 Peptic Activity

Peptic aggression is determined by acid and by pepsin. There are no methods to measure pepsin directly. The relevance of in vitro proteolytic activity of pepsin to peptic aggression in vivo is uncertain.

The measurement of peptic activity is relatively difficult, is not standardized, and is complicated by the fact that the pepsins and their precursors are heterogeneous proteins that differ in their physicochemical, biochemical and immunochemical characteristics, and in their cellular origins. There are two immunochemically distinct types of pepsinogen in man: pepsinogen I, which is derived primarily from the chief cells in fundic mucosa, and, pepsinogen II which is produced by chief cells in the pyloric glands in the gastric antrum (81). Pepsinogens are converted to their respective enzymes, pepsin I (pepsin) and pepsin II (gantricsin).

The pepsin concentration in gastric juice is conventionally estimated by determining the rate at which a sample of this fluid hydrolyzes a protein substrate, usually bovine hemoglobin at a single pH. The peptic activity of gastric juice is not necessarily proportionate to total pepsin concentration, since the pepsins do not have the same optimal pH and since they differ in their specific activities. In vitro measurements of the level of peptic activity produced by different pepsins against substrates may not indicate the level of peptic activity that is experienced by the mucosa in vivo.

Pepsin-acid Relationship

Hydrochloric acid is required for the activation of pepsin. Pepsinogen secretion from the chief cells in response to stimulation is modulated by gastric acid (49). This effect is believed to be mediated through a local cholinergic reflex. Acid is required for the conversion of pepsinogen to pepsin. Peptic activity is optimal at acidic pH, although this optimal pH varies for different pepsins in their specific activities for different proteins, but none of the pepsins exhibits proteolytic activity above pH 5.0. Acid denatures proteins and makes them more susceptible to peptic digestion. The products of peptic digestion stimulate gastrin release which in turn stimulates further secretion of acid and pepsinogen. Pepsinogen is stimulated by similar secretagogues that stimulate acid output.

A marked reduction of the peptic activity of gastric juice could be obtained by inhibiting pepsinogen secretion or acid secretion. It was shown that the stimulation of pepsin release by food is dependent on intact vagal innervation (38). By using human hemoglobin as substrate, it has been shown that peptic activity is influenced by pH. The optimal pH for peptic activity was shown to be at pH 1-1.6 and at pH 3.6 (13).

2.8 Mucosal Defense Mechanism

Mucosal defense mechanism is a functional description of an interplay between several factors that may be important in protecting the gastric mucosa against the potentially damaging effects of gastric contents. The normal gastric mucosa has a great capacity to resist H^+ back diffusion, inspite of the high concentration gradient between the lumen and the blood. This property of the mucosa which resists acid back diffusion and mucosal injury is called the "gastric mucosal barrier". This barrier may be considered as a series of physico-chemical barriers dependent on several interacting factors. The main components of the gastric mucosal barrier are: the surface epithelium, the surface mucus layer, the mucosal bicarbonate secretion, and the mucosal blood flow.

A two component barrier consisting of the mucus layer lining the gastric mucosa and the adjacent layer of the surface epithelium was proposed by Hollander (43). Subsequently, Davenport suggested that the gastric mucosal barrier is formed by the apical membrane of the epithelial cell together with the tight junctions which prevent the H^+ ion back diffusion (19). The idea of the possible role of mucus in protecting the gastric mucosal epithelium was introduced by Heatley (40). The unstirred water layer also influences the access of H^+ to the membrane and along with the mucus it may form a mucus-bicarbonate layer through which diffused H^+ is neutralized by bicarbonate secreted from the gastric mucosa (101).

The gastric mucosa is a tight epithelium and is one of the most impermeable membranes in the body. The lipoprotein apical membrane constitutes a major barrier to potentially damaging agents. This barrier is formed by the apical membrane of the surface epithelial cells, along with the tight junctions which prevent the diffusion of ions (19). The luminal acid diffuses into the mucosa when the barrier property is broken. Approximately half a million cells are lost from the gastric mucosa each minute and the surface epithelial cells have a life span of 2-6 days. A balance between cell loss and cell replication is essential for maintenance of barrier integrity.

The mucus is secreted from surface epithelial cells and mucus neck cells in the gastric gland. The mucus forms a gel adhering to the surface of the gastric mucosa. A lubricating action of gastric mucus is known to protect the mucosa from mechanical abrasion. Mucus also provides the mixing barrier for the diffused H^+ and the secrete HCO_3^-. The gel forming and viscous properties of mucus depend on undegraded glycoprotein. This undegraded glycoprotein complex is a polymer of four glycoprotein subunits which are joined by disulfide bridges linking their protein cores (4). This undegraded glycoprotein is susceptible to proteolysis.

The function of the gastric mucus is determined by its concentration and structure of glycoprotein. Both the depth and structure of the surface mucus are important in protecting gastric mucosa. The thickness of the surface mucus is determined by the dynamic balance between the rate of mucus secretion and erosion by peptic digestion. The production of the mucus gel depends on its rate of secretion, the concentration of undegraded glycoprotein, and by the ratio of undegraded and degraded glycoprotein subunits. Mucus gel erosion depends on the rate of proteolysis by pepsin and by the mechanical removal of mucus.

Previous studies suggested the active bicarbonate (HCO_3^-) transport from the gastric mucosa (26,74). HCO_3^- secretion can be demonstrated when acid secretion is blocked by an H_2 receptor antagonist. The HCO_3^- mucus barrier implies that the luminal H^+ is separated from epithelial HCO_3^- by an unstirred mucus layer through which H^+ diffuses slowly and is neutralized by HCO_3^-. The pH gradient across the mucus layer from acidic pH on the luminal side to neutrality on the epithelial side was demonstrated by using a pH microelectrode (6).

The mucosal blood flow may also play a role in the mucosal defense. It may maintain intramural pH by removing, diluting or buffering the acid load from back diffusion. The mucosal metabolic and secretory states are also maintained by the gastric microcirculation.

The protecting role of these gastric mucosal defense factors has been proposed based on evidence that agents which alter the mucosal defense mechanism are injurious to the gastric mucosa. The injurious effect of aspirin and ethanol on the gastric mucosa may be related to their action on mucus depletion. The role of mucosal defense is also supported by the protecting action of agents that improve mucosal resistance, such as prostaglandins. Inspite of the accepted role of this mucosal defense, its pathophysiologic role in peptic ulcer disease is not known.

Only recently has there been increasing interest in the role of mucosal defense in peptic ulcer disease. Several agents that improve mucosal defense have been shown to be effective in the healing of peptic ulceration. Hitherto, the approach to therapy of peptic ulcer disease has been aimed mainly at gastric acid reduction. A section on medical management of uncomplicated peptic ulcer disease in adults is given in the appendix.

3. COMPARATIVE EFFECTS OF TWO CIMETIDINE REGIMENS ON 24-HOUR INTRAGASTRIC ACIDITY IN PATIENTS WITH ASYMPTOMATIC DUODENAL ULCER

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SUMMARY

The effect of 600 mg of cimetidine given twice daily on 24-hour intragastric hydrogen ion (H^+) concentration was compared with that of the standard regimen of 300 mg of cimetidine given four times daily in six patients with asymptomatic duodenal ulcer. According to the double-blind, Latin-square, repeated-measures design, all subjects followed each cimetidine regimen and a placebo regimen for one week. Acid secretion studies and determinations of drug and gastrin levels in the blood were carried out on the last day of each treatment week.

Although 600 mg of cimetidine BID suppressed H^+ after breakfast and during the night, compared with placebo treatment ($P < 0.01$), the 300-mg QID regimen suppressed H^+ only after breakfast and supper ($P < 0.05$). A higher percentage of pH readings $\geq$ 3.0 were obtained with 600 mg of cimetidine BID than with 300 mg of cimetidine QID during the night ($P < 0.05$); compared with percentages when placebo was taken, the percentages of pH readings $\geq$ 3.0 were greater both overnight and during a 24-hour period only when 600 mg of cimetidine was given BID ($P < 0.01$).

The observed difference in intragastric H^+ suppression after each regimen could not be explained by variations in serum concentrations of cimetidine or serum concentrations of gastrin. Despite similar peaks of serum cimetidine after evening doses of 300 or 600 mg of cimetidine, nocturnal intragastric acidity was lower in subjects given 600 mg BID. Further, H^+ levels after lunch were similar in both cimetidine-treated groups, despite markedly higher serum cimetidine concentrations in patients receiving 600 mg BID. Pharmacokinetic studies showed equivalent elimination half-times and 24-hour areas under the curve of

serum cimetidine concentration in patients on the two cimetidine regimens. Postprandial integrated gastrin responses were of similar magnitude in patients on either cimetidine regimen. There was no significant difference in mean serum gastrin concentrations during the night in placebo-treated and cimetidine-treated patients. Only a weak correlation was observed between H^+ and serum gastrin concentration. Although a fluctuation of the H^+:gastrin ratio occurred after each meal in all groups, the ratio was suppressed by both dosages of cimetidine.

The findings suggest that a regimen of 600 mg of cimetidine BID is superior to the standard regimen of 300 mg QID in suppressing intragastric acidity in patients with asymptomatic duodenal ulcer.

INTRODUCTION

Cimetidine administered daily in four equal doses produces a striking and consistent decrease in intragastric acidity in normal subjects[1] and is effective in the management of patients with duodenal ulcer.[2,3] In North America the standard dosage of cimetidine is 300 mg QID. Because patient compliance might be encouraged by a simplified dosage regimen, we investigated the antisecretory effects and pharmacokinetic properties of cimetidine in dosages of 600 mg BID and 300 mg QID in patients with asymptomatic duodenal ulcer disease.

MATERIALS AND METHODS

Study Design

In the double-blind, repeated-measures, unbalanced Latin-square study design, six patients received each of the following treatments (in random order) for one week: 300 mg of cimetidine QID, 600 mg of cimetidine BID, and placebo. All medications were taken orally. Acid secretion studies and determinations of blood levels of drug and gastrin were carried out on the last day of each treatment week.

The study was approved by the Ethics Committee of the Department of Medicine, University of Alberta, and informed consent was obtained from each patient.

Patients

Each of the six patients had a duodenal ulcer confirmed by endoscopy but was asymptomatic and was not receiving treatment for the ulcer at the time of the study (Table 1). The mean age of the patients was 39 years; the mean duration of duodenal ulcer disease was 9.6 years. Two patients had previously experienced upper gastrointestinal hemorrhage, and one patient had had a perforation treated by a patching procedure six years prior to the study. All patients were free of endocrine, respiratory, hepatic, neurologic, renal, cardiovascular, hematologic, and allergic diseases, and none had a history of gastric resection or vagotomy. None drank excessive amounts of alcohol, but five patients were smokers who continued to smoke during the study. Results of a physical examination, routine laboratory screen (complete blood count, SMA-6, SMA-12, and urinalysis), chest roentgenogram, and electrocardiogram of each patient were normal.

Before entry into the study, each patient was given a pentagastrin test (6 ug/kg subcutaneously). The mean (± SE) basal acid output (BAO) was 4.1 ± 1.5 mEq/hr, but the BAO exceeded 5 mEq/hr in two subjects. The mean maximal acid output (MAO) in response to pentagastrin was 41.5 ± 5.9 mEq/hr, the MAO values in four subjects exceeding 35 mEq/hr. The mean peak acid output was 39.1 ± 5.7 mEq/hr.

Trial Procedure

Patients were randomly assigned to a specific treatment schedule on day 1 and received 300 mg of cimetidine QID, 600 mg of cimetidine BID, or placebo QID (Table 2). They returned on day 7 for gastric acid secretion studies, began the next treatment in their sequence on day 8, and returned on day 14 for gastric acid secretion studies. The last regimen in the sequence began on day 15, and final gastric acid analyses were conducted on day 21.

Subjects were hospitalized, in a special ward that was set aside for their use, at 7:00 (on the 24-hour clock) on days 7, 14, and 21. All subjects fasted for 12 hours before the gastric acid secretion studes; water ad libitum was permitted during the fast. When the gastric acid secretion studies began, a strict protocol was followed (Table 3). A nasogastric tube was positioned under fluoroscopic control so that the tip was in the most dependent part of the stomach. Intravenous infusion of a 0.9% saline solution was then initiated at a rate sufficient to keep the vein open and to allow free access for sampling of venous blood for determination of serum cimetidine and serum gastrin concentrations. (Approximately 750 ml of saline was infused, and less than 250 ml of blood was drawn, during each 24-hour period). Residual stomach contents were aspirated, and a control sample of 5 ml of blood was taken. At 8:30, patients received a standard meal and their first dose of drug or the placebo. The placebo or subsequent doses of the drug were given with meals at predetermined times (Table 2).

Gastric acidity was monitored by a method similar to that described by Pounder et al[1]: 5-ml samples of gastric juice were aspirated at 30-minute intervals while the patient was awake and at 60-minute intervals while the patient was asleep. A 5-ml flush of the 0.9% saline solution was used, when necessary, to obtain sufficient fluid for pH assessment and to wash the syringe used to aspirate gastric juice. With a combined glass and reference electrode and pH meter, the pH of the sample was measured to the nearest 0.10 unit, after which the sample was returned to the stomach. At the time of gastric pH analysis, a 5-ml sample of venous blood was drawn through the IV line for serum separation and storage at -37 °C.

All vital signs and subjective symptoms were monitored and recorded every eight hours during the study. The subjects were ambulatory, ate their meals at a table, and entertained themselves by talking, reading, watching television, knitting, playing games, and walking about the ward. At the end of the 24-hour study period, the IV line and nasogastric tube were removed. The patients were instructed about the medications to be taken during the next week and were told to return any unused medication on the next study day.

Food Intake

The subjects could select foods from two menus (Table 4) that provided identical volume and identical amounts of carbohydrate, fat, and protein. The number of calories and the relative proportions of macronutrients varied from meal to meal, but this meal pattern was chosen to reflect usual eating habits. Each meal was consumed in 15 minutes. Only snacks of known composition were allowed between meals. The volume of liquid consumed was recorded, and detailed individual logs of cigarette consumption (permitted ad libitum) were kept.

The patients consumed an average of 1.659 kcal/day, comprising an average of 183 gm of carbohydrate, 85 gm of protein, and 65 gm of fat. Approximate proportions of all calories provided by carbohydrate, protein, and fat, respectively, were 44%, 21%, and 35%. There was no difference in food intake during each of the three periods. The average daily intake of fluids was 1.9 L. The five subjects who smoked had an average of 11.4 cigarettes per day.

Hydrogen Ion (H^+) Activities and pH Profiles

Standard tables were used to convert the results of each pH measurement to H^+ activity. Mean H^+ concentrations (derived from the same tables) for each treatment group after breakfast, lunch, and supper, as well as overnight (22:30-8:30) and for the 24-hour period, were compared. The pH profile of each treatment group was compared by using the cumulative percentage of pH readings at or above values ranging from 1.0 to 7.0.

Serum Cimetidine Concentration

The serum cimetidine concentration was measured by the high-pressure liquid chromatographic method of Soldin et al.[5] Mean serum cimetidine levels were plotted against the time period for the two cimetidine-treated groups. The area under the curve (AUC) after each dose was determined by the trapezoidal rule from time 0 (dose administration) to infinity. The concentration from the previous dose that was present at time 0 was accounted for by calculating the area from this concentration-time point to infinity and subtracting it from the overall AUC after the dose. The overall elimination rate constant (K_E) and elimination half-life of each subject were determined by means of linear regression analysis from the terminal portion of the concentration-time curve.

The ratio of H^+ activity to serum cimetidine concentration (H^+:C) during the 24-hour study period was compared in the two cimetidine-treated groups. Each mean H^+ wsa plotted against the mean serum cimetidine concentration to determine the relationship between the serum drug level and gastric acid suppression.

Gastrin Measurements

The Schwarz-Mann commercial radioimmunoassay kit was used to determine serum gastrin concentrations (ng/L). The integrated gastric response (IGR) after each meal was calculated by obtaining the AUC using the trapezoidal rule from time 0 (time of meal) to 120 minutes. The basal concentration, present at time 0, was accounted for by calculating the area from this concentration to 120 minutes and subtracting it from the overall AUC after each meal. The following equation was used to calculate postprandial IGR:

$$\text{IGR} = t \quad \frac{a+b}{2} + \frac{b+c}{2} + \ldots\ldots \frac{d+e}{2} \quad - aT$$

The a, b, ... e represent serum gastrin concentrations in sequential order, a being the concentration when the meal was given. The t is the interval of time between each determination of serum gastrin level; T is the total time period for the calculated postprandial IGR. The ratio of H^+ to serum gastrin concentration during the 24-hour study period was compared in the three groups. The relationship between serum gastrin concentration and H^+ was studied to determine whether cimetidine would alter it.

Statistical Analysis

Descriptive statistics concerning each variable were calculated for each of the three treatment groups. For these analyses, intragastric pH measurements were converted to H^+ concentration, using the tables of Moore and Scarlata,[4] assuming the ($Na^+ + K^+$) concentration to be 50 mEq/L. As Moore and Scarlata have pointed out, H^+ activity is significantly different fromm H^+ concentration at pH levels usually found in gastric juice, but H^+ concentration is commonly accepted as an index of gastric secretion.

The data examined were the mean pH at each observation point, the mean H^+ concentration after each meal and dose up to the next meal or snack, and the frequency of occurrence of pH levels ≥ 3.0 during the night and during the total 24-hour observation period. At pH ≥ 3.0, peptic activity is reduced to about 70% of maximum,[6] consequently improving the milieu for ulcer healing.

Mean intragastric H^+ concentrations at sampling times in patients on each regimen were compared by an analysis of variance, which took into account variations in subjects, periods, and regimens. The occurrence of residual effects from doses taken earlier was examined, but no evidence of such effects was found.

Data on the frequency of occurrence of pH ≥ 3.0 during the night and during the 24-hour study period were analyzed by an Arcsin transformation; treatment regimens were compared using an analysis of variance.[7]

Graphs showing pH, H^+, serum cimetidine concentrations, serum gastrin concentrations, and different ratios of these variables were plotted for each treatment group for the 24-hour study period.

RESULTS

Intragastric H^+ Concentrations

Graphic representation of the mean pH at each observation point over the 24-hour period (Figure 1) shows postprandial elevation of pH regardless of treatment. Postprandial increases in pH were higher during cimetidine administration than during placebo dosing. Mean H^+ concentrations equivalent to the pH measurements during periods after meals and after the bedtime dose are shown in Table 5 and in Figure 2. At each period the mean H^+ concentration is highest for the placebo regimen, and there is an obvious decrease following each dose of cimetidine. The effect of the QID regimen was significantly different from that of placebo only after breakfast and supper ($P < 0.05$). A significant reduction ($P < 0.01$) in H^+ concentration followed the breakfast dose and the bedtime dose of 600 mg of cimetidine. In terms of intragastric H^+ concentrations, there was no statistically significant difference between the two cimetidine regimens at any observation period.

When the frequency of pH measurements ≥ 3.0 during the night was examined (Table 6 and Figure 3), the response of patient 3 was noteworthy because the intragastric pH was $\geq$ 3.0 only once during the night after any of the treatments. When the frequency of elevated pH during the 24-hour period was examined (Table 7), three patients (1, 2, and 6) had a greater frequency of pH $\geq$ 3.0 durng the 600-mg BID regimen than during the 300-mg QID regimen. In each of these patients, the frequency of pH elevation during the night was considerably greater after 600 mg than after 300 mg of cimetidine (Table 6), accounting for this difference between the two regimens. This effect of the 600-mg BID regimen of cimetidine was significantly different from that of either the 300-mg QID regimen ($P < 0.05$) or placebo ($P < 0.01$) during the night (Table 6) but was significantly superior only to placebo ($P < 0.01$) during the 24-hour period (Table 7).

Pharmacokinetics of Cimetidine

Results of the pharmacokinetic measurements made after each dose of cimetidine are given in Tables 8 and 9. Figure 4 shows serum cimetidine concentration curves for each patient. Although certain intersubject and intrasubject variations are evident, the overall pattern is consistent in all patients and agrees with the findings of others.[8]

Peak serum cimetidine concentrations (C_{max}) were attained within 0.5 to 3.0 hours (T_{max}) of administration, indicating a rapid absorption rate regardless of dosage. Although C_{max} values were fairly consistent after each 300-mg dose, this value was generally higher after morning 600-mg doses than after evening 600-mg doses — evident in patients 5 and 6, especially. The mean C_{max} of the morning 600-mg doses was significantly higher than that of the evening 600-mg doses (4.63 vs 3.08

μg/ml), but this difference did not result in a significant difference in AUC values. Patients 5 and 6, however, had substantially higher AUCs after the morning doses than after the afternoon doses. Although the mean C_{max} after the evening cimetidine dose was greater with 600 mg than with 300 mg (3.08 vs 2.25 μg/ml), this difference was not significant.

There was no significant difference between patients receiving the 300-mg and 600-mg doses in the time to peak cimetidine concentration (T_{max}). After the morning dose of 300 mg of cimetidine, the serum cimetidine concentration remained above 0.5 μg/ml for 11.1 hours and above 1.0 μg/ml for 7.0 hours (Table 8). The serum cimetidine concentration was greater than 0.5 and 1.0 μg/ml for longer periods after the morning than after the evening 300-mg dose ($P < 0.005$). In contrast, the serum cimetidine concentration after the evening dose of 600 mg remained above 0.5 and 1.0 μg/ml for 7.2 and 4.5 hours, respectively, but shorter intervals were observed after the morning dose of 600 mg (Table 9). The 24-hour AUC and the apparent steady-state concentration of cimetidine were similar in patients receiving 300 mg QID and those receiving 600 mg BID. The half-life of cimetidine ranged from 1.78 to 3.91 hours, with no significant difference between the two regimens.

Serum Gastrin Concentration

The mean fasting serum concentration of gastrin was similar in patients receiving placebo, 300 mg of cimetidine QID, and 600 mg of cimetidine BID (Figure 5). In patients receiving placebo, serum gastrin concentrations increased consistently after each meal, the average postprandial rise being approximately 95%. Postprandial increases of serum gastrin were higher in both cimetidine-treated groups, with average increases of 169% and 135%, respectively, in subjects receiving 300 mg QID and 600 mg BID. The peak serum gastrin concentration occurred within 60 minutes of each meal in the three groups. There was no significant intergroup difference in mean serum gastrin concentration during the night (Figure 5).

The IGRs over 120 min were significantly higher ($P < 0.05$) in both cimetidine-treated groups than in the placebo group only after the 8:30 dose (Table 10). Although there was a tendency toward higher IGRs in cimetidine groups than in the placebo group after lunch and supper, the differences were not statistically significant. When the two cimetidine groups were compared, the IGRs after each meal were not significantly different.

Relationships Between Intragastric H^+, Serum Cimetidine, and Serum Gastrin Concentrations

With the regimen of 300 mg of cimetidine QID, the ratio of H^+ to serum cimetidine concentration (H^+:C) increased slightly after each meal (Figure 6). The average H^+:C ratio was higher during the 12-hour period after the 20:30 dose than after the three meals, but this difference was not statistically significant. With the regimen of 600 mg of cimetidine BID, the H^+:C ratio increased progressively after each meal. The following differences in patients receiving 600 mg BID were significant ($P < 0.05$): breakfast vs lunch, lunch vs supper, breakfast vs supper. The mean H^+:C ratio with 600 mg of cimetidine BID was significantly higher than with 300 mg QID only after lunch and supper ($P < 0.05$).

In subjects receiving placebo, the mean ratio of intragastric H^+ to serum gastrin concentration (H^+:G) showed a biphasic response after each meal, with a decline, a rise, and a later decline occurring over a 2.5-hour period (Figure 7). When 300 mg of cimetidine was given QID, there was a similar pattern of H^+:G ratios after each meal, except that the postprandial increases were lower than those in subjects receiving placebo. With 600 mg of cimetidine BID there was a marked suppression of the H^+:G ratio after breakfast ($P < 0.05$). The H^+:G ratio was similar in subjects receiving 600 mg of cimetidine BID and those receiving 300 mg QID, and the H^+:G ratios after each meal were lower in the two cimetidine groups than in the placebo group. The mean overnight H^+:G ratio was significantly higher ($P < 0.05$) in subjects receiving placebo than in those receiving either dosage of cimetidine.

There was a weak but significant negative correlation between intragastric H^+ and serum cimetidine concentration in patients receiving either dosage of cimetidine ($r = -0.48$, $P < 0.01$ with 300 mg QID and $r = 0.48$, $P < 0.01$ with 600 mg BID). A weak negative correlation was also noted between intragastric H^+ and serum gastrin concentration in the cimetidine groups ($r = -0.45$, $P = 0.049$ with 300 mg QID and $r = -0.44$, $P = 0.055$ with 600 mg BID). There was a weak but significant negative relationship between H^+ and serum gastrin concentration in the placebo group ($r = -0.65$, $P < 0.01$).

DISCUSSION

Serial measurements of intragastric pH during a 24-hour period are useful for studies of the effects of drugs or diet on gastric acidity because such measurements are likely to reflect H^+ activity in the stomach as affected by factors of daily living.[1,9-11] Studies using the Latin-square design — each subject serving as his or her own control — reduce intersubject variability and allow for more sensitive assessment of an antisecretory regimen.

Peterson and coworkers[11] used a similar technique to test the effects of "extra effort" drug regimens on 24-hour intragastric acidity in patients with inactive duodenal ulcer. In their study as well as ours, fewer than 10% of the pH readings in the placebo group were $\geq$ 3.0 during the day, overnight, or throughout the 24-hour study period. In both studies, about 30% of daytime pH readings were $\geq$ 3.0 in patients treated with 300 mg of cimetidine QID. In contrast to the findings of Peterson et al,[11] the present study found a lower percentage of pH readings $\geq$ 3.0 during sleep and throughout the 24-hour period in patients receiving 300 mg of cimetidine QID. Although the explanation for differences is not clear, the mean peak acid output in response to pentagastrin (6 µg/kg) was greater in the patients studied by Peterson et al than in ours: 46.8 vs 39.1 mEq/hr. In the study by Peterson et al, double-dose cimetidine (600 mg QID, with meals and at bedtime) was compared with standard cimetidine therapy (300 mg QID, with meals and at bedtime). This "extra effort" (double-dose) regimen was significantly better than the standard cimetidine regimen in reducing intragastric acidity during the daytime, but it did not have the same effect during the hours of sleep.

In the present study, both cimetidine regimens provided 1,200 mg/day, or only half as much cimetidine as the double dose provided by Peterson et al. In our study, gastric acidity during the hours of sleep and after breakfast was significantly less with 600 mg of cimetidine BID than with 300 mg of cimetidine QID. This improvement was effected simply by changing the schedule of dosing without altering the total daily dose.

The present study found that, compared with placebo, the cimetidine regimen using 600-mg doses significantly reduced the mean H^+ concentration after the bedtime dose and after the breakfast dose; the regimen using 300-mg doses resulted in significant reductions in acidity, compared with the effects of placebo, after the breakfast and supper doses. Intragastric pH $\geq$ 3.0 occurred more frequently during the 24-hour period with the cimetidine regimen of 600 mg BID than with the usual regimen of 300 mg QID. The 24-hour effect of the 600-mg BID regimen on pH levels was significantly different from that of placebo, the differences being attributable to the marked effect of the 600-mg dose during the night, when pH values $\geq$ 3.0 occurred significantly more often than after placebo or a dose of 300 mg of cimetidine. The marked effect of the 600-mg BID regimen on intragastric acidity during the night has clinical significance because it provides a milieu conducive to healing of duodenal ulcers.

The results suggest that consumption of three moderate-sized meals and three snacks daily was sufficient to stimulate gastric acid secretion during the waking hours, with little advantage gained from the buffering effects of the food. Interestingly, all six subjects commented that they received more food during the trial than they would normally have eaten at home. It is possible that the normal daily food intake of the subjects, all of whom were asymptomatic at the time of the study, was less indeed than that provided in the present experiment. However, the mean caloric intake during the study was about two thirds of that provided for normal subjects or duodenal ulcer patients in other studies.[1,9,10] Furthermore, the menus provided only decaffeinated coffee and no alcohol; cigarettes ad libitum were permitted.

The variation in the pattern of inhibition of H^+ concentration was not related to differences in serum cimetidine concentrations: H^+ after lunch and supper was similar in both cimetidine groups, despite marked differences in serum cimetidine concentrations (Figure 4). With either regimen, there was only a weak correlation between serum cimetidine concentrations and H^+. The H^+:C ratios after meals varied widely between patients receiving 300 mg QID and those receiving 600 mg BID (Figure 6), despite similar H^+ values. After the evening dose of cimetidine, the pharmacokinetic parameters were similar in subjects receiving 300 mg QID and those given 600 mg BID (Tables 8 and 9), but the H^+ concentration was lower in the latter group. These observations are in accord with those of Festen et al,[12] who found no significant correlation between serum cimetidine level and the outcome of treatment with this H_2-receptor blocker in patients with peptic ulcer.

The different patterns of H^+ activity after the 300-mg and 600-mg doses were not explained by variations in serum gastrin concentrations, because the postprandial rise in serum gastrin was similar in both groups (Figure 5). However, the relationship between changes in serum gastrin concentration and intragastric H^+ must be reexamined: in the placebo group there was only a weak negative correlation between these variables, and there was an unexpected fall in the H^+:G ratio two hours after meals. Furthermore, in subjects on either of the cimetidine regimens there was only a weak relationship between serum gastrin concentrations and H^+, the late postprandial fall in H^+:G ratio persisted (Figure 7), and, despite lower H^+ activity in patients receiving 600 mg BID than in patients receiving 300 mg QID (Figure 2), overnight serum gastrin concentrations were similar in the two groups (Figure 5).

Just as diurnal variations in the pharmacokinetics of other drugs have been described,[13] differences between patterns after nighttime versus daytime doses were observed in this study: there was no significant reduction of H^+ after 300 mg of cimetidine taken at night (Figure 2), and the mean peak serum cimetidine concentration after the nighttime 600-mg dose was only 67% as high as the mean peak serum cimetidine level after the morning dose (Table 9). The peak serum cimetidine concentration after 600 mg of cimetidine tended to be lower in the evening than in the morning (Figure 4). It is not likely that this difference was related to food intake that accompanied the morning dose because peak serum cimetidine concentrations were similar after each 300-mg dose of cimetidine.

Bodemar et al[14] have failed to show a difference in the AUC after a single dose of 200 mg of cimetidine taken with food and a comparable dose taken after fasting, but they did not make comparisons at different times of the day. Since no significant differences were noted in the T_{max} or the half-life of cimetidine after morning and evening doses of

600 mg, the observed reduction in C_{max} values during the evening may be attributed to diminished absorption. Patients 5 and 6, who showed the greatest differences in their morning and afternoon C_{max} values with 600 mg of cimetidine, also had substantially smaller AUCs after the evening dose than after the morning dose (Table 9).

Lower overnight levels of H^+ after a 600-mg dose than after a 300-mg dose (Figure 2), despite similar serum cimetidine concentrations (Figure 4), suggest that the sensitivity of the parietal cell to an H_2-receptor antagonist may vary between morning and night. Although the explanation for the lack of correlation between H^+ activity and serum cimetidine concentrations has not been determined in this study, the prolonged inhibitory effect of 600 mg of cimetidine taken in the morning, despite low serum concentrations of the drug, suggests that the serum concentration does not necessarily reflect the concentration of drugs at the H_2 receptor on the parietal cell.

Normal release of gastrin after the ingestion of food is modulated by acid inhibition of further gastrin release. In the patients given placebo, the gastrin concentration rose an average of 95% after each of the three meals. Postprandial gastrin release was much greater in cimetidine-treated subjects (Figure 5), presumably reflecting drug-induced inhibition of acid secretion — thus permitting a greater release of gastrin. Overnight basal secretion of acid probably is not under close control by gastrin, because serum gastrin concentrations were similar with placebo and the 300-mg and 600-mg doses of cimetidine. The greater inhibition of overnight H^+ effected by 600 mg of cimetidine, compared with 300 mg (Figure 2), is not related to serum gastrin or serum cimetidine concentrations (Figure 4). However, the overnight H^+:G ratio with 600 mg of cimetidine BID (Figure 7) suggests that sensitivity of the parietal cell to gastrin is influenced by 600 mg of cimetidine, or that some other factor influenced by cimetidine also influences overnight H^+ activity.

In patients receiving placebo, the H^+:G ratio fell from a high in the basal state to a low after dinner (Figure 7), suggesting that sensitivity of the parietal cell to gastrin varies during the day or that the roles of factors other than gastrin vary in a diurnal fashion. The H^+:G ratio is greatly influenced by cimetidine, but the diurnal variation persists: in patients given 300 mg of cimetidine QID, the ratio is highest overnight, lowest after lunch and supper, and of intermediate value after breakfast. The low values after lunch and supper correspond with the lowest values of H^+ in patients receiving 300 mg of cimetidine QID (Table 5). In contrast, in patients receiving 600 mg of cimetidine BID, the H^+:G ratio was lowest after breakfast and highest after supper (Figure 7), corresponding to the lowest and the highest values of H^+ activity (Table 5). Thus the dosage schedule influenced the height of the serum cimetidine peak (Figure 4), the serum gastrin peak (Figure 5), the inhibition of acid concentration (Table 5), the postprandial gastrin concentration (Table 10), and the H^+:G ratio (Figure 7).

Cimetidine has been proven to be safe and efficacious in the treatment of duodenal ulcers.[2,3] The standard regimen in North America is 300 mg QID. The greater inhibitory effect of twice-daily cimetidine on gastric acid secretion, shown in the present study, provides a rational basis for the use of 600 mg of cimetidine BID in the treatment of symptomatic patients with endoscopically demonstrated duodenal ulcers. A similar trial comparing the efficacy of 300 mg of cimetidine QID and 600 mg of cimetidine BID has just been completed in Canada, and the results suggest that the two regimens are equivalent in the healing of symptomatic duodenal ulcers.[15]

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Table 1. Patient characteristics

Patient No.	Age	Sex	Duration of Disease (Years)	Results of One-Hour Pentagastrin Stimulation* BAO (mEq/hr)	MAO (mEq/hr)	PAO (mEq/hr)	TAO (mEq/hr)	Total Volume (ml)	Mean H^+ Concentration (mmol/L)
1	52	F	27	1.5	20.4	18.0	13.6	217	63.3
2	61	M	0.3	1.6	33.2	31.8	27.2	207	132.0
3	39	M	13	8.0	48.0	46.8	38.2	367	101.5
4	25	M	3	8.9	60.8	54.2	33.9	184	177.5
5	23	F	9	0.1	36.0	33.0	18.1	191	71.5
6	35	F	5	4.2	50.8	50.8	40.1	306	106.9

* BAO = basal acid output: total volume aspirated before administration of pentagastrin; MAO = maximal acid output: four times the highest 15-minute output; PAO = peak acid output: twice the sum of the two highest successive 15-minute outputs; TAO = total acid output during the hour after administration of pentagastrin; total volume = volume aspirated during the hour after administraion of pentagastrin; mean H^+ concentration = mean of the concentration in each of the four 15-minute aspirates.

Table 2. Regimens.

	Cimetidine (C) and Placebo (P)		
Time	600 mg C, BID	300 mg C, QID	Placebo
8:30	C300	C300	P
	C300	P	P
12:30	P	C300	P
	P	P	P
17:30	P	C300	P
	P	P	P
20:30	C300	C300	P
	C300	P	P

Table 3. Protocol followed on days 7, 14, and 21.

Time	Procedure	Measurements, Samples
7:00	Nasogastric tube placed; fluoroscopy of tube position; IV infusion	
8:30	Breakfast; treatment	
10:30	Morning snack	Gastric pH measured and 5 ml of blood drawn every 30 min from 8:30 to 22:30
12:30	Lunch; treatment	
14:30	Afternoon snack	
17:30	Supper; treatment	
20:30	Bedtime snack; treatment	
22:30	Optional bedtime snack	Gastric pH measured and 5 ml of blood drawn every 60 min from 22:30 to 8:30
8:30	Last gastric sample taken; nasogastric tube and IV infusion removed	

Table 4. Menus from which patients selected meals.

Menu A	Menu B
Breakfast -- 8:30	
20 gm Special K	46 gm whole wheat toast
141 gm 2% milk	5 gm butter
12 gm whole wheat toast	92 gm scrambled egg
5 gm butter	20 gm jam or
48 gm scrambled egg	14 gm jam and 4 gm sugar
5 gm bacon (fried crisp)	150 ml orange juice
20 gm jam or	300 ml coffee (decaffeinated), tea, or water
14 gm jam and 4 gm sugar	
100 ml orange juice	
300 ml coffee (decaffeinated), tea, or water	
Morning snack -- 10:30	
2 gm Arrowroot biscuits	
300 ml coffee (decaffeinated), tea, or water	
Lunch -- 12:30	
76 gm tossed salad with	50 gm coleslaw
15 gm thousand island dressing	12 gm coleslaw dressing
43 gm hot sliced ham	50 gm roast beef
100 gm mashed potato	87 gm rice
5 gm butter	5 gm butter
100 gm carrots	53 gm mixed vegetables
130 gm canned peaches	68 gm fresh banana
300 ml coffee (decaffeinated), tea, or water	300 ml coffee (decaffeinated), tea, or water
Afternoon snack -- 14:30	
38 gm oatmeal cookies	
300 ml coffee (decaffeinated), tea, or water	
Supper -- 17:30	
234 gm chicken noodle soup, turkey salad sandwich plate	100 gm vegetable soup, tuna sandwich plate
33 gm ice cream	100 gm fresh orange
300 ml coffee (decaffeinated), tea, or water	300 ml coffee (decaffeinated), tea, or water
Bedtime snack -- 20:30	Bedtime snack -- 22:30 (optional)
28 gm cheddar cheese	150 gm orange juice
14 gm graham wafers	
or	
28 gm cheddar cheese	
71 gm fresh apple	
300 ml coffee (decaffeinated), tea, or water	

Table 5. Mean H^+ concentration after meals and at bedtime.

Treatment	Breakfast	Lunch	Supper	Bedtime
Cimetidine				
300 mg QID	10.52*	3.55	7.93*	15.72
600 mg BID	4.18†	10.28	17.79	7.05†
Placebo	25.78	17.90	20.14	23.40

* $P < 0.05$, compared to placebo.

† $P < 0.01$, compared to placebo.

Table 6. Frequency of occurrence (in absolute numbers and, parenthetically, in percents) of pH $\geq$ 3.0 at night (after last dose and snack).

Patient No.	Cimetidine 300 mg QID	Cimetidine 600 mg BID	Placebo
1	2/13 (15)	14/14 (100)	5/14 (36)
2	4/14 (29)	13/14 (93)	4/14 (29)
3	0/14 (0)	1/14 (7)	0/14 (0)
4	1/14 (7)	3/14 (21)	0/14 (0)
5	10/14 (71)	8/14 (57)	2/14 (14)
6	2/14 (14)	9/14 (64)	0/14 (0)
Mean (%)	22.8	56.8*†	13.1

* $P < 0.05$, compared to 300 mg of cimetidine QID,

† $P < 0.01$, compared to placebo.

Table 7. Frequency of occurrence (in absolute numbers and, parenthetically, in percents) of pH $\geq$ 3.0 during 24-hour period.

	Cimetidine		
Patient No.	300 mg QID	600 mg BID	Placebo
1	13/39 (33)	22/39 (56)	11/39 (28)
2	8/39 (21)	30/39 (77)	8/39 (21)
3	5/39 (13)	4/39 (10)	1/39 (3)
4	10/39 (26)	5/39 (13)	4/39 (10)
5	20/39 (51)	17/39 (44)	5/39 (13)
6	9/39 (23)	20/39 (51)	0/39 (0)
Mean (%)	27.8	41.8*	12.5

* P < 0.01, compared to placebo.

Table 8. Results of pharmacokinetic measurements after 300-mg doses of cimetidine at 8:30, 12:30, 17:30, and 20:30.

Patient	T_{max} (hr)				C_{max} (µg/ml)				Half-Life* (hr)	AUC* (mg.hr/L)	AUC_{0-24} (mg·hr/L)	C_{ss} (mg/L)	Duration of Serum Concentration >0.5 µg/ml		> 1.0 µg/ml	
No.	8:30	12:30	17:30	20:30	8:30	12:30	17:30	20:30	20:30	20:30			8:30	20:30	8:30	20:30
1	1.0	1.0	0.5	1.0	3.49	3.08	2.52	3.26	3.79	7.43	34.50	1.44	12.0	7.0	10.4	5.2
2	2.5	1.0	1.0	3.0	1.20	2.67	1.92	1.63	2.72	6.46	21.32	0.89	10.8	8.3	4.4	3.4
3	0.5	0.5	1.0	1.0	2.11	2.11	1.85	2.72	2.99	5.01	27.93	1.16	12.0	7.0	9.5	4.5
4	1.5	0.5	1.0	1.0	2.11	2.14	1.87	3.37	3.15	5.64	20.88	0.87	10.0	5.5	5.7	1.8
5	1.0	1.0	1.0	2.0	2.03	2.49	1.54	1.51	3.63	7.05	23.62	0.98	10.7	8.2	6.9	2.9
6	0.5	1.5	0.5	3.0	1.60	1.93	1.24	0.99	--	--	17.97	0.75	11.2	6.2	5.3	0
Mean	1.2	0.9	0.8	1.8	2.09	2.40	1.82	2.25	3.26	6.32	24.37	1.02	11.1	7.0	7.0	3.0
SEM	0.3	0.2	0.1	0.4	0.31	0.18	0.17	0.41	0.20	0.45	2.44	0.10	0.3	0.4	1.0	0.8

* The half-life and AUC could not be determined for the first three doses because cimetidine levels were insufficient during the terminal phase as a result of the short intervals between doses. Because of insufficient cimetidine levels, the half-life and AUC could not be estimated for patient 6.

Table 9. Results of pharmacokinetic measurements after 600-mg doses of cimetidine at 8:30 and 20:30.

											Duration of Serum Concentration			
Patient	T_{max} (hr)		C_{max} (µg/ml)		Half-Life (hr)		AUC (mg.hr/L)				>0.5 µg/ml		> 1.0 µg/ml	
No.	8:30	20:30	8:30	20:30	8:30	20:30	8:30	20:30	AUC_{0-24} (mg.hr/L)	C_{ss} (mg/L)	8:30	20:30	8:30	20:30
1	1.5	1.0	6.98	5.98	2.27	3.51	17.42	14.21	34.80	1.45	7.1	7.2	4.4	4.5
2	1.5	3.0	3.06	2.41	2.70	2.47	10.52	12.41	23.04	0.96	5.8	7.6	4.4	4.7
3	1.0	1.5	3.97	2.71	2.48	3.91	14.25	13.11	26.65	1.11	7.2	8.8	5.0	5.6
4	1.0	1.0	3.35	3.29	2.67	1.81	8.03	9.52	16.42	0.68	3.9	5.6	2.4	3.6
5	1.5	1.5	6.16	1.91	2.20	2.54	16.19	11.58	27.21	1.13	6.5	8.0	4.4	4.5
6	1.5	3.0	4.28	2.20	1.78	2.16	11.04	8.95	20.01	0.83	5.5	6.1	3.6	3.9
Mean	1.3	1.8	4.63	3.08*	2.35	2.73	12.91	11.63	24.69	1.03	6.0	7.2	4.0	4.5
SEM	0.1	0.4	0.70	0.61	0.14	0.33	1.47	0.84	2.62	0.11	0.5	0.5	0.4	0.3

* $P < 0.05$, 8:30 vs 20:30

Table 10. Mean (± SE) postprandial integrated gastrin responses (ng·min/L).

Time	Placebo	Cimetidine 300 mg QID	Cimetidine 600 mg BID
8:30-10:30	2,715 ± 576	6,205 ± 1,106*	7,570 ± 1,722*
12:30-14:30	4,358 ± 1,192	9,303 ± 2,271	7,218 ± 1,519
17:30-19:30	2,468 ± 2,532	10,433 ± 2,216	6,230 ± 1,561

* $p < 0.05$, compared to placebo.

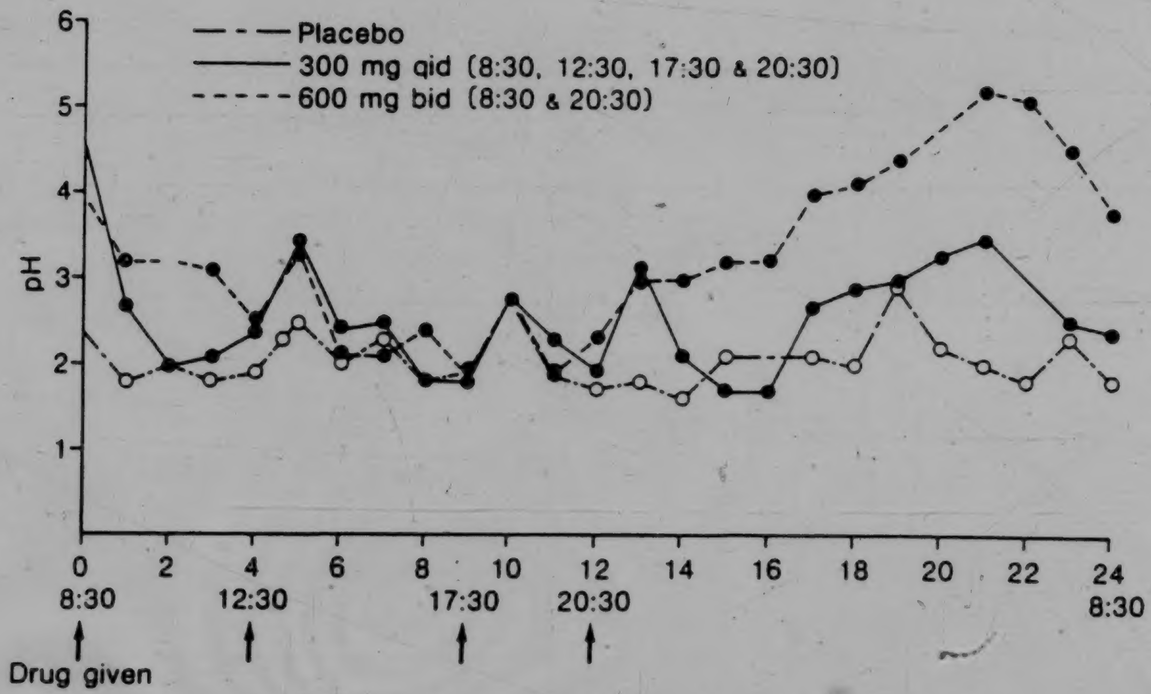

Figure 1. Mean intragastric pH values of the three groups during a 24-hour interval.

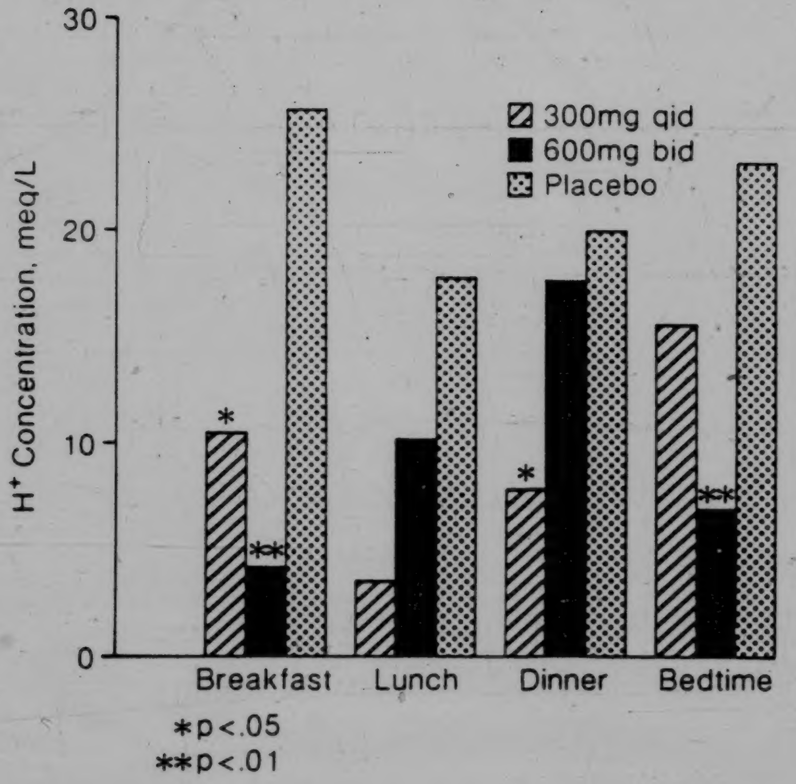

Figure 2. Mean H^+ concentrations of the three groups after meals and at bedtime. Significant differences from concentrations in patients receiving placebo are indicated by *(P < 0.05) and ** (P < 0.01).

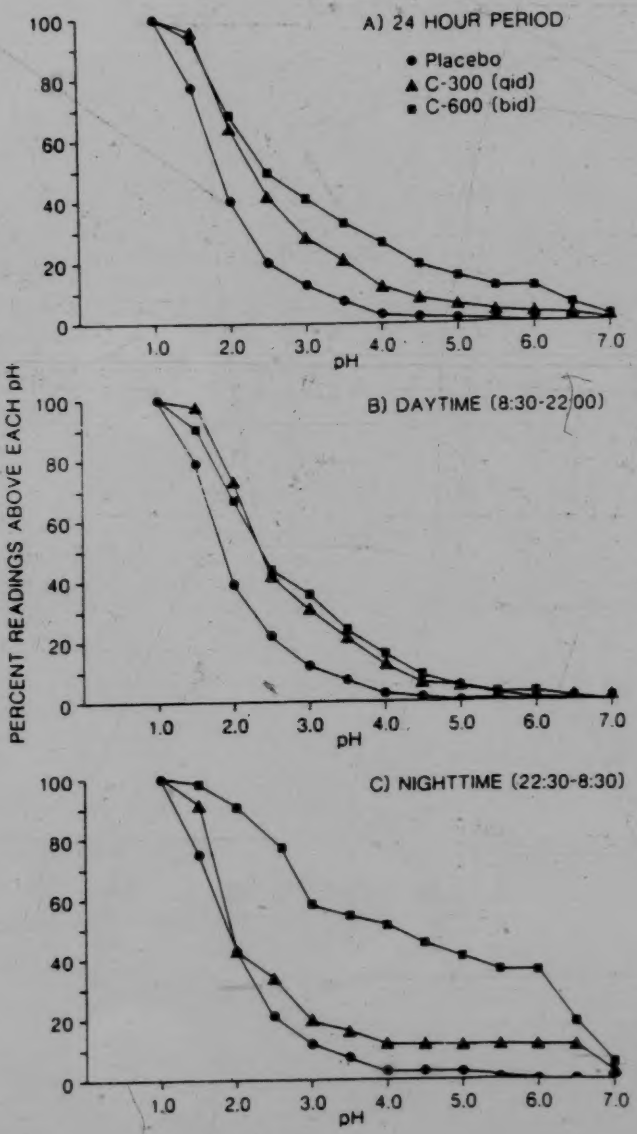

Figure 3. Cumulative percentage of pH readings above each value in the three groups during three periods of time. (● = placebo, ▲ = 300 mg of cimetidine QID, and ■ = 600 mg of cimetidine BID).

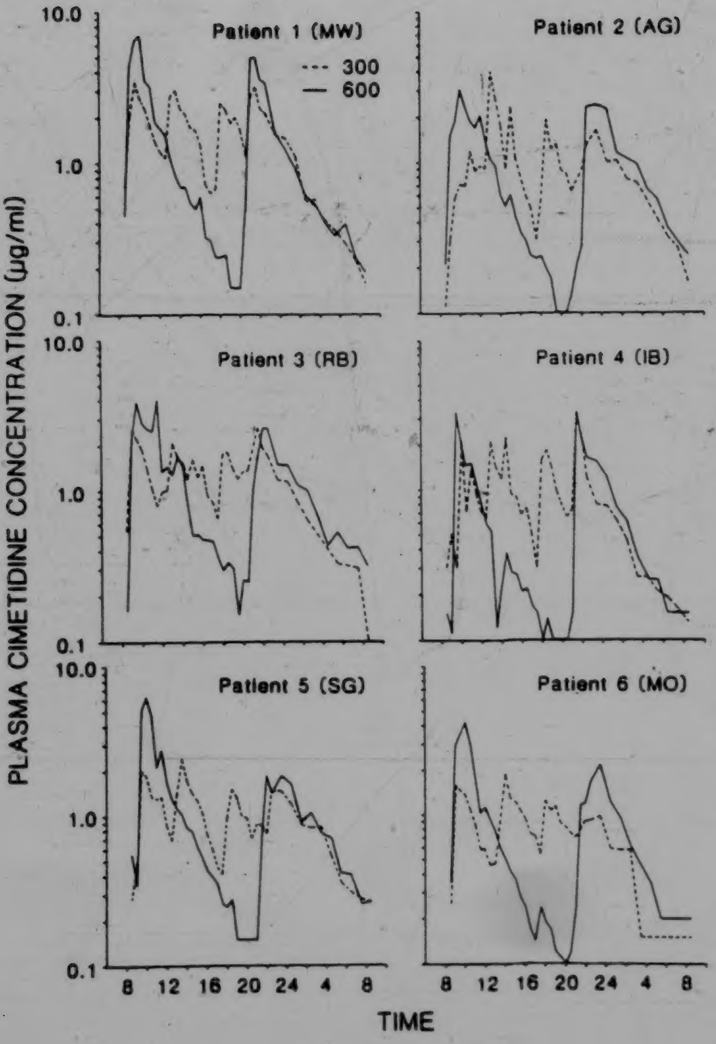

Figure 4. Twenty-four hour pattern of serum cimetidine concentrations in individual patients during treatment with 300 mg QID (- - -) and 600 mg BID (——).

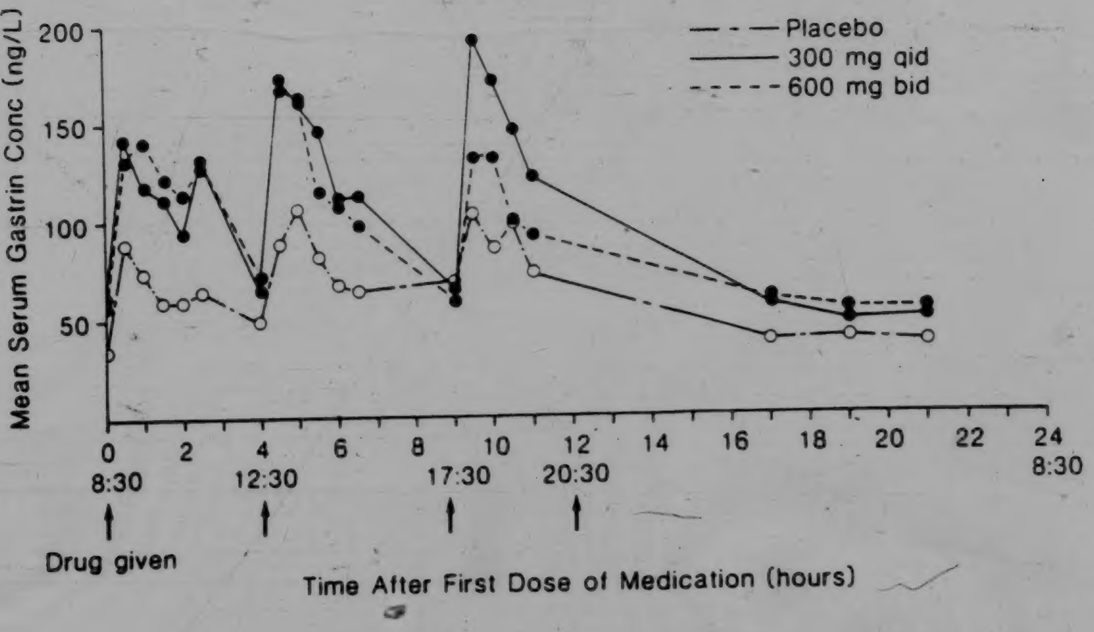

Figure 5. Twenty-four hour pattern of mean serum gastrin concentrations in the three groups.

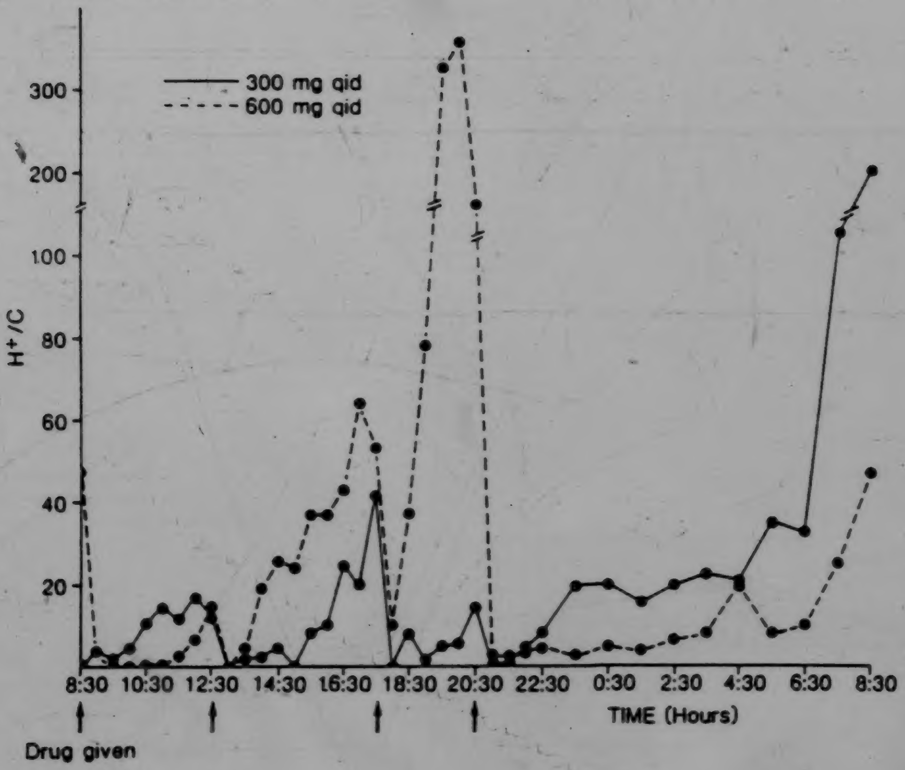

Figure 6. Twenty-four hour pattern of the ratio of intragastric H^+ concentration to serum cimetidine concentration (H^+:C) in patients given 300 mg of cimetidine QID (——) or 600 mg of the drug BID (- - -).

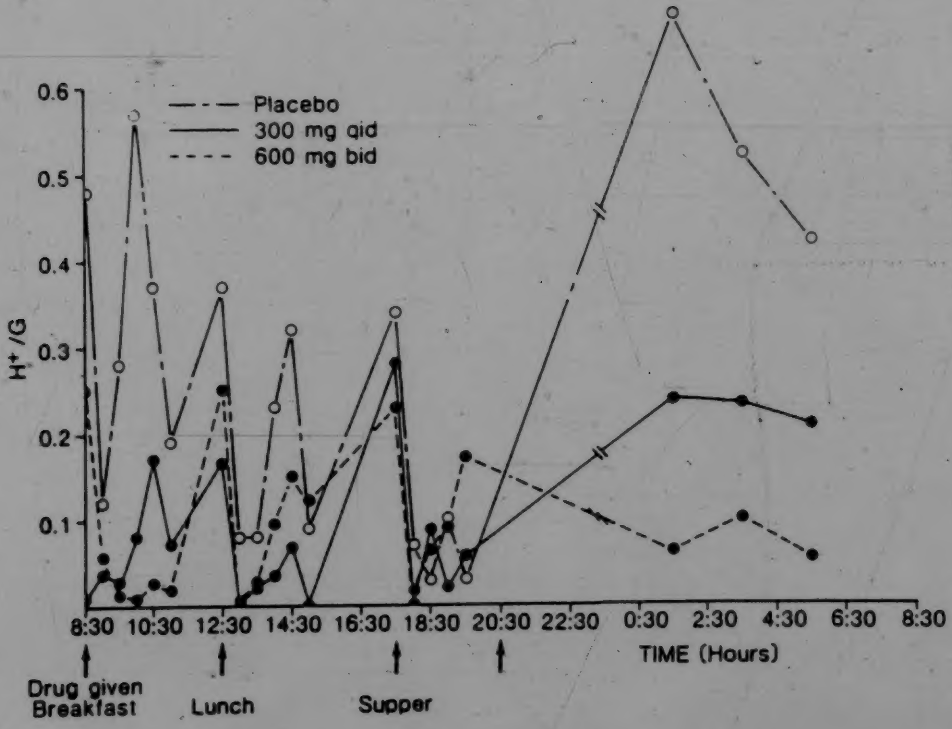

Figure 7. Twenty-four hour pattern of the ratio of H^+ to serum gastrin concentration (H^+:G) in the three groups.

4. COMPARISON OF COMBINATION OF MYLANTA II AND CIMETIDINE ON 24-HOUR INTRAGASTRIC ACIDITY IN PATIENTS WITH ASYMPTOMATIC DUODENAL ULCER DISEASE

SUMMARY

This study was undertaken to determine the effect of antacid and cimetidine, alone and in combination, on 24-hour intragastric hydrogen ion activity (H^+) and serum gastrin profiles. Eight patients with duodenal ulcer disease were studied using a Latin square design. Mylanta II given 1 and 3 hr pc and hs combined with 600 mg bid cimetidine (C+A7) produced more suppression of H^+ after breakfast, overnight, and over the 24-hour period when compared to Mylanta II 7 times daily (A7). Antacid given 4 times daily after lunch and supper combined with cimetidine bid (C+A4) maintained the neutralizing capacity during this time, although C+A4 was not as effective as C+A7. However C+A4 produced more suppression of nocturnal H^+ as compared with antacid alone (A7). A higher percentage of the readings at or above pH 4.0 were obtained with C+A7 as compared to A7 or C+A4. A greater postprandial integrated gastrin response (IGR) was obtained in all treatment groups as compared with placebo. The mean peak cimetidine concentration (Cmax) was higher but the time to peak (Tmax) was shorter after the morning than after the evening dose. The area under the cimetidine concentration-time curve (AUC), Cmax and Tmax values after the morning and evening doses of cimetidine were not affected by the co-administration of antacid. In conclusion 1) combination therapy of cimetidine plus antacid is more effective than antacid alone in the reduction of intragastric H^+; 2) antacid alone fails to suppress the overnight intragastric acidity; 3) antacid given concurrently with cimetidine does not interfere with pharmacokinetic parameters of plasma cimetidine concentration.

INTRODUCTION

Peterson and co-workers have demonstrated that the "extra-effort" regimen of cimetidine plus antacid, or cimetidine plus antacid plus an anticholinergic agent, was superior to standard cimetidine therapy (300 mg qid) in reducing gastric hydrogen ion activities[1]. Cimetidine 600 mg twice a day is superior to standard cimetidine 300 mg four times a day in reducing intragastric H^+ after breakfast, overnight, and over the 24-hour period[2]. The present study was undertaken to determine: 1) if this twice a day regimen of cimetidine could be further improved with antacid taken 4 or 7 times daily; 2) if potent high-dose antacid therapy was as effective as cimetidine taken twice daily in reducing H^+; 3) if the 24-hour serum gastrin profile is influenced by antacid and cimetidine; and finally, 4) if antacid influences the pharmacokinetics of cimetidine given twice daily.

METHODS

STUDY DESIGN

A double-blind, repeated measures, Latin Square Design was used in which each subject received all possible treatments in a sequential random order. Each treatment was administered on a separate occasion for one week each with intragastric pH monitoring, gastrin and drug level determinations carried out on the last day of each treatment week.

This study was approved by the Ethics Committee of the Department of Medicine at the University of Alberta and informed consent was obtained from each patient.

STUDY POPULATION

Eight patients with a history of duodenal ulcer previously documented by endoscopy or barium meal X-ray were studied. The mean duration of their disease was 3.9 years. They were all asymptomatic at the time of entering into the trial and were not receiving any treatment for duodenal ulcer at that time. There were 7 males and 1 female with a mean age of 40.6 years (range 28-67 years). Four patients had previously experienced upper gastrointestinal hemorrhage controlled by medical therapy. All of the patients were free of significant systemic disease and had no past history of gastric surgery or vagotomy. Physical examination, routine laboratory tests (CBC, biochemical profiles, urinalysis), chest X-ray and ECG of each patient did not show any significant change during the study period. The mean basal acid output (BAO) obtained prior to the study was 6.9 ± 1.5 (SEM) mmol/hr (range 1.9 - 14.8 mmol/hr). In response to pentagastrin (0.6 μg/kg) given subcutaneously, the mean maximal acid output was 47.0 ± 5.7 (SEM) mmol/hr (range 28.0 - 68.8 mmol/hr); only two out of eight patients had MAO less than 30.0 mmol/hr.

TRIAL PROCEDURE:

On the study day (Day 7, 14, 21, and 28), the patients were hospitalized in a specially allocated hospital ward at 7:00 am following a 12 hour overnight fast. A strict protocol was then followed (Table 1): a nasogastric tube (size 14 French) was positioned under fluoroscopic control so that the tip was in the most dependent part of the stomach. An intravenous infusion of 0.9% saline was then initiated at a rate sufficient to keep the vein open to allow for subsequent sampling of venous blood for determinations of gastrin and cimetidine concentrations. Residual stomach contents were aspirated and the pH of the gastric sample was measured to the nearest 0.10 unit using a combined glass and reference electrode and pH meter (Canlab), which had been calibrated with pH 2.00, 4.00 and 7.00 buffers. Patients received a standardized meal and their first dose of cimetidine or identical placebo at 8:30 am. The subsequent doses of cimetidine and antacids or identical placebo were given at predetermined times as indicated in Table 2. Gastric acidity was monitored over the 24-hour period: five ml samples of gastric juice were aspirated every 30 minutes while the patient was awake (8:30 - 22:30 hr) and every hour during the hours of sleep (22:30 - 8:30 hr). The gastric sample was then returned to the stomach to ensure complete absorption of cimetidine and complete acid-buffering potential of the antacid. Venous samples were obtained and centrifuged, and the plasma was immediately separated and stored at -4°C for further analyses of gastrin and cimetidine concentrations. All subjective symptoms observed during the study period were recorded.

Each pH reading was converted to hydrogen ion activity (H^+) from standard table[3]. The Schwarz-Mann commercial radioimmunoassay kit was used for the determination of serum gastrin concentration (pg/ml). This measures both G-34 and G-17. The method used to calculate the integrated gastrin response has been published[2]. Plasma cimetidine concentration (mg/ml) was measured by using a modified reverse-phase, high-pressure liquid chromatography method[4]. The pharmacokinetic parameters of cimetidine given with different doses of antacid were studied from the plasma concentration-time curves.

FOOD INTAKE AND ACTIVITIES

The subjects were provided with standarized meals[2] with identical composition of carbohydrate, fat and protein between the four trial periods. Each meal was consumed over a 15 minute period. Regular snacks of known composition were allowed between meals. The patients consumed an average of 1890 kcal/day, comprised of 232 gm carbohydrate, 82 gm protein, and 70 gm fat. The proportion of the total calories provided by carbohydrate protein and fat were 60%, 22% and 18% respectively. There was no difference in food intake between the four trial periods. The average fluid intake per day was 2.4 L. Three of the eight subjects smoked an average of 14.6 cigarettes per day. No change in smoking habits was recorded during the study. All subjects were ambulant and encouraged to maintain their activities on the ward.

MEDICATION REGIMENS

Each patient received four treatment regimens (Table 2) for one week each in a sequential random order. Mylanta II (composition: magnesium hydroxide 350 mg, aluminium hydroxide 650 mg, and simethicone 30 mg per 5 ml; with an acid neutralizing capacity of 31.6 mmol per 5 ml) 30 ml was given seven times daily, one and three hours after each meal and at bedtime, either alone (A7) or in combination with cimetidine 600 mg administered twice daily (C+A7). The combination of cimetidine 600 mg twice daily and Mylanta II 30 ml given four times daily, one and three hours after lunch and supper (C+A4) was also studied. The identical placebo of cimetidine tablet and liquid antacid were used to maintain double-blind conditions.

PHARMACOKINETICS OF PLASMA CIMETIDINE

The cimetidine pharmacokinetic parameters were calculated in the C+A7 and C+A4 groups. The maximum plasma concentration (Cmax) and the time of its occurrence (Tmax) were obtained from the measured values. The elimination half-life ($t\,^1\!/_2$) was calculated from the terminal slope (β) determined by linear regression analysis. The area under plasma cimetidine-concentration time curves following the morning and evening doses of cimetidine from time zero (i.e. dose administration) to infinity were calculated by the trapezoidal method, and adding the area obtained by dividing the last plasma concentration by the terminal slope (β). The concentration from the previous dose present at time zero was taken into account by calculating the area from this concentration-time point to infinity, and subtracting it from the overall AUC after the dose. Because of the variability of some of the concentration-time points, the $t_{1/2}$ and AUC of some curves were not measured.

STATISTICAL ANALYSIS

A repeated measures analysis of variance was applied to test the difference between all treatment groups. Pairwise comparisons were made only if there was an overall difference. The frequency distribution of the pH readings at or above 4.0 in each group was tested using chi-square analysis. Student's t-test was employed to compare with pharmacokinetic parameters between the treatment regimens.

RESULTS

In the placebo-treated patients, the intragastric pH ranged between 1.8 - 2.9 over the 24 hour period, with some fluctuation in pH occurring after meals (Figure 1). When antacid was given one and three hours after each meal and at night (A7), the intragastric pH values were higher during the daytime and during the early hours of sleep. Combining seven times a day antacid with cimetidine 600 mg bid (C+A7) was associated with a much higher pH as compared with the placebo and with the A7 groups. This difference was striking during both the daytime and during the night. When cimetidine 600 mg bid was combined with antacid taken four times a day, one and three hours after lunch and one and three hours after supper (C+A4), the pH values were intermediate between the low values seen in the placebo group, and the high values seen in the C+A7 group (Figure 1).

In the placebo-treated patients, the intragastric H^+ activities progressively fell after meals from 14.11 ± 1.20 mmol/L after breakfast, to 6.29 ± 0.49 after supper (Table 3). The H^+ activities were also significantly lower than in the placebo group for A7, C+A7, and C+A4 after breakfast, after lunch, after supper, and over the 24 hour period (Figure 2). Both C+A7 and C+A4 significantly suppressed intragastric H^+ activities overnight ($p<0.05$). The H^+ activities were lower ($p<0.05$) in C+A7 than in A7 after breakfast, after lunch and over the 24 hour period. The H^+ activities were significantly lower in C+A7 than in C+A4 only after lunch (Table 3).

Since peptic activity is greatly diminished at pH 4.0[5], the frequencies of occurrence of pH levels equal to or greater than this pH during the 24-hour period, during the daytime and during the night were compared between all treatment groups. In the placebo-treated patients, less than 4% of the readings were at or above pH 4 during all time periods (Figure 3). The highest percentage of pH readings at or above 4.0 was observed in C+A7 at all time periods, with the value of 63% during the 24 hour period and during the daytime, and 57% overnight. In contrast, the percentage of readings at or above pH 4.0 was similar in the A7 and C+A4 groups during the 24 hour period and during the daytime; these values were intermediate between the lower percentage values in the placebo group and the high percentage values in the C+A7 group ($p<0.05$). During the night, a higher percentage of the pH readings at or above pH 4.0 was obtained in C+A7 and C+A4 as compared to the placebo group ($p<0.05$). There was no significant difference of cumulative percentages of the pH readings of pH >4.0 between A7 and placebo during the night. The higher percentage of pH readings >4.0 was observed in C+A7 than in C+A4 or A7 during the night, but only the difference between C+A7 and A7 was significant.

In a previous study, intragastric H^+ activities in the cimetidine 600 mg bid group (C) were significantly lower than in the placebo group after breakfast, overnight and over the 24 hour period[2]. As expected, the percentage of H^+ activities as compared with placebo were similar in C[2] versus C+A4 after breakfast and overnight. In contrast, the addition of antacid after lunch was associated with a dramatic reduction in this value, from 63% in C to 17% in C+A4 (2, and Figure 2). A similar inhibitory effect of antacid was seen after supper. The H^+ activities expressed as a percentage of placebo values was even lower when antacids were given following cimetidine given at breakfast (11% versus 21%, C+A7 versus C+A4, respectively, $p<0.05$). This ratio was approximately similar in A7, C+A4 and C+A7 following lunch and following supper.

SERUM GASTRIN CONCENTRATION

In the placebo-treated patients, the serum gastrin concentration rose by approximately 100% after each meal (Figure 4). In all groups, a greater gastrin response was observed after each meal. This elevation was more prolonged following supper, and the overnight gastrin concentrations were significantly higher in A7, C+A7, C+A4 than in the placebo-treated patients: the mean overnight gastrin concentration was 27.9 ± 0.4 pgm/ml in the placebo-treated patients, compared with 51.9 ± 7.8 pgm/ml in A7, 50.3 ± 5.2 pgm/ml in C+A7, and 46.2 ± 3.2 pgm/ml in C+A4.

The integrated gastrin response (IGR) after each meal was calculated over the time period that the concentration approached its basal value by using the trapezoidal rule. The IGR was calculated over 4 hour period after breakfast and after lunch, and over 7 hour period after supper as the gastrin response was more prolonged during this time. The 4 hour IGR were higher in C+A7, C+A4, and A7 as compared with placebo after breakfast and after lunch, although the difference failed to achieve significant level. Higher IGR over 7 hours after supper was observed in C+A7, C+A4 and A7 groups than in placebo, but the difference was not significant.

RELATIONSHIP BETWEEN H^+ AND SERUM GASTRIN CONCENTRATION

Marked fluctuations in the ratio of intragastric H^+ to serum gastrin concentrations (H^+/G) were observed in the placebo group (Figure 5). The H^+/G was significantly lower in the three treatment groups (A7, C+A7 and C+A4) as compared with the placebo group. Overnight, the value of H^+/G was markedly higher in placebo and A7 than in C+A7 or C+A4 ($p<0.05$). After 00:30 hour, the H^+/G rose dramatically in the patients given one dose of antacid alone before bedtime (A7).

CIMETIDINE PHARMACOKINETICS

The profiles of the mean plasma cimetidine concentration-time curves following the morning and evening doses of 600 mg cimetidine combined with antacid seven times a day (C+A7) or four times a day (C+A4) are shown in Figure 6. There were considerable interindividual variations of pharmacokinetic data for cimetidine (Table 5). Following the morning dose of cimetidine in C+A7, the peak plasma concentrations (Cmax) was attained within 3.0 hr of administration, with the mean time to peak (Tmax) of 1.8 ± 0.2 hr. The Cmax following the morning dose of cimetidine in C+A7 was twice as high as the Cmax following the evening dose ($p<0.05$). Similarly, the cimetidine concentration at 2 hr (C_2) following cimetidine administration was higher in the morning than in the evening. Although the Tmax values were generally longer following the evening than the morning dose of cimetidine in C+A7, the difference failed to show statistical significance. Higher Cmax and C_2 values following the morning than the evening doses were again observed in C+A4, and the Tmax values were longer following the evening than the morning dose. There was no difference of Cmax or C_2 between C+A7 and C+A4 for both the morning and evening periods. Our previous study showed similar diurnal variation of cimetidine concentration when cimetidine 600 mg bid was given by itself[2]. The Cmax and Tmax values after the morning and the evening doses in this present study were similar to those in patients treated with cimetidine alone[2]. The obseved AUC from time zero to infinity were numerically higher following the morning dose than the evening dose in both C+A7 and C+A4, although the difference was significant only in C+A4 ($p<0.05$). The AUC $0-\infty$ were similar in C+A7 and C+A4, both following the morning and evening doses of cimetdine. These values were similar to those in our previous study where cimetidine was given alone[2]. Similar values of cimetidine concentration at 10 hr after administration (C_{10}) following the morning and evening doses of cimetidine were obtained in both C+A7 and C+A4. There was no difference of C_{10} between C+A7 and C+A4 during the morning and evening periods. The 24 hr. area under the curve (AUC $_{0-24}$) were similar in the two treatment regimens. These values were not different than the AUC_{0-24} observed when cimetidine was given as 600 mg bid in our previous study[2].

DISCUSSION

A diurnal variation was noted in the intragastric H^+ following meals (Figure 2). This appeared to be unrelated to the composition of the meal, since the calories and protein intake following breakfast was less than that taken at suppertime. In spite of this, the H^+ activity following supper is less than half of that observed following breakfast. It is uncertain whether this fluctuation in H^+ activity was due to a diurnal variation associated with feeding, or to some other factor. On examining the results of individual patients, the greater acid response following breakfast than supper was observed in 6 out of the 8 patients. The explanation for this diurnal variation has not been established in this study. This observation has at least two important implications. First, the effect of an antisecretory agent studied first thing in the morning is not necessarily of the same quantitative magnitude as the other time of the day. Secondly, a therapeutic regime must be selected to achieve greater acid inhibition in the morning rather than later in the day time.

The widely-accepted dosing regime for antacids is to administer the medication 1 and 3 hours after meals and at night[6]. The present study confirmed the potent acid-neutralizing effect of giving Mylanta II 1 and 3 hours after meals (Figure 2). The H^+ activity associated with giving antacid 1 and 3 hours after breakfast was 35% of the placebo value, and giving the same amount of antacid after lunch and supper was also associated with lower H^+ activities: H^+ activity was 16% of the placebo value after lunch, and 41% of the placebo value after supper. Thus, both the qualitative and quantitative effects of antacids on the neutralization of gastric acid are influenced by the time of day. While it is generally recommended to take antacid at night, nighttime antacid was associated with only a 33% reduction in H^+ activity. Nonetheless, antacid taken at bedtime in the A7 group was associated with a fivefold increase in the percentage of readings at or above pH 4.0. during the night. Therefore, this study confirms the recommendation to use antacid following meals and at night.

Peterson and co-workers[1] have previously shown that the combination of cimetidine and antacid (with or without an anticholinergic) is superior to the standard dosage regimen of cimetidine (300 mg qid) during the daytime and over 24 hour period. We wished to determine whether the combination of antacid and cimetidine was also superior when cimetidine was given twice daily. In the C+A7 group, antacid was taken 1 and 3 hours after meals, but cimetidine was added at breakfast as well as at bedtime. At breakfast, the mean H^+ activity was significantly lower with the combination of cimetidine plus antacid 1 and 3 hours after breakfast than with antacid or cimetidine alone. However, this beneficial effect was lost after supper, i.e. there was no difference between H^+ activity at this time in A7, C+A7 or C+A4 (Table 3). Thus the "added effect" of using cimetidine bid plus antacid was beneficial over antacid alone mainly following breakfast. This was surprising, since the effect of the cimetidine given with breakfast was expected to have been lost by lunch, and most certainly by suppertime. However, since the H^+ activity falls between breakfast and suppertime (Table 3), less antisecretory or neutralizing effect is required later in the daytime.

One dose of antacid taken at bedtime (A7) was associated with a modest reduction in H^+ activity but the value was not significantly different than the placebo value (Table 3). The combination of nighttime antacid with cimetidine (C+A7) was associated with a significantly lower H^+ activity, 3.63 ± 0.72 mmol/L, a value which represents only 23% of the placebo value of 15.83±1.03 mmol/L. Indeed, H^+ activity overnight was lower in the group given cimetidine with antacid, than in the group given antacid alone (Table 3). We have previously demonstrated lower intragastric H^+ activity after breakfast and overnight when cimetidine is taken twice daily (600 mg bid) compared with cimetidine given four times a day (300 mg qid)[2]. In this study we have shown that the H^+ can be further reduced by the added effort of taking antacid (C+A7). Thus, it is recommended that when combination therapy is being considered, antacids should be taken 1 and 3 hours following the breakfast dose of cimetidine, and with the evening dose of cimetidine.

For the purpose of patient compliance, we examined the effect of two doses of antacid after lunch and supper when combined with cimetidine taken at breakfast and at bedtime. This regime (C+A4) was not as effective as giving antacid more frequently (C+A7): H^+ was numerically higher after breakfast, after lunch, overnight and over the 24 hour period in C+A4 compared with C+A7 (Table 3). It is possible, however, that the combination of less frequent doses of antacid in combination with cimetidine might have been more effective if antacid had been taken 1 and 3 hours after breakfast and at bedtime rather than 1 and 3 hours after lunch and after supper.

With the acid reduction achieved using cimetidine and/or antacid, the serum gastrin concentrations were greater in A7, C+A7, C+A4 groups than in the placebo group (Figure 4). Just as there were diurnal variations in H^+ (Figure 1), so also were there differences in the IGR following each meal, with higher values following supper than following breakfast (Table 4). This resulted in a different ratio of H^+ to gastrin concentration after each meal (Figure 5). This suggests that the sensitivity of the parietal cell and G-cell to food stimulation may vary throughout the day. It is also possible that the sensitivity of the G-cell to feedback inhibition by acid varied throughout the day.

Some previous studies have suggested that the co-administration of antacid interferes with the absorption of cimetidine[7]. However, the data to support this observation has been conflicting[8]. From our study, we failed to show a difference in pharmacokinetic parameters of cimetidine in C+A7 and C+A4 both following the morning and the evening doses of cimetidine. Antacid was given 1 and 3 hr after the morning cimetidine dose, and concurrently with cimetidine at night in C+A7. In C+A4, antacid was not given after the morning dose of cimetidine and was given 2 hr prior to the nighttime dose. A diurnal variation in cimetidine concentration was observed. In both groups lower AUC $0-\infty$ was observed following the evening than the morning doses of cimetidine. This observation can not be explained by the co-administration of antacid with cimetidine at night in C+A7, as a similar pattern was observed in C+A4 where the cimetidine was taken at night without antacid. This observation of diurnal variation of cimetidine kinetics was similar to our previous study when cimetidine 600 mg was given twice a day[2].

The H^+ activities following breakfast were more suppressed in C+A7 than in C+A4 (Figure 2) in spite of the similar values of Cmax and AUC $0-\infty$. This suggests that antacid given 1 and 3 hr after cimetidine enhances the acid suppressing effect by maintaining acid neutralizing capacity without interfering with pharmacokinetic properties of cimetidine. Antacid given concurrently with cimetidine at night time, as in C+A7, provides an additional effect in suppressing intragastric H^+ overnight.

The combination of antacids 7 times daily with cimetidine twice daily (C+A7) was associated with the lowest H^+ after breakfast, overnight and during the 24 hour period (Table 3). The highest percentage of pH readings above pH 4.0 were observed in this group during the daytime, overnight and over the 24 hour period (Figure 3). Unfortunately, all the subjects taking antacids seven times daily experienced troublesome loosening and increased frequency of their bowel motions. This diarrhea might discourage patient compliance if the antacid 7 times a day regime (A7) is recommended for a prolonged treatment period. Future study must now be performed to establish whether the use of less frequent or lower dosage of antacid might achieve this beneficial effect on acid suppression when cimetidine is combined with antacid.

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Table 1

TRIAL PROCEDURE

TIME	PROCEDURE	SAMPLING
07:00	NG tube placed under fluoroscopy. 0.9 saline I.V. infusion.	
08:30	Breakfast; cimetidine or placebo	
09:30	Antacid or identical placebo.	
10:30	Morning snack.	
11:30	Antacid or identical placebo.	
12:30	Lunch.	
13:30	Antacid or identical placebo.	gastric pH measurement every 30 min from 08:30 to 22:30 and serial blood samplings
14:30	Afternoon snack.	
15:30	Antacid or identical placebo.	
17:30	Dinner.	
18:30	Antacid or identical placebo.	
20:30	Antacid or identical placebo.	
22:30	Optional bedtime snack, cimetidine plus antacid or identical placebo.	gastric pH measurement every 60 min from 22:30 to 08:30 and serial blood samplings
08:30	Last gastric sample taken, NG tube and IV infusion removed.	

Table 2

MEDICATION REGIMENS

MEDICATION REGIMENS	DOSAGE AND SCHEDULE
High-potency antacid (A7).	Mylanta II, 30 ml given 1 and 3 hr after meals and at bedtime (22:30 hr).
Twice daily cimetidine plus frequent antacid (C + A7).	Cimetidine 600 mg bid (8:30 and 22:30 hr) plus Mylanta II 30 ml given 1 and 3 hr after meals and at bedtime (22:30 hr).
Twice daily cimetidine plus lower dose antacid (C + A4).	Cimetidine 600 mg bid (8:30 and 22:30 hr) plus Mylanta II 30 ml given 1 and 3 hr after lunch and supper.
Placebo control (P).	Identical cimetidine placebo given twice daily plus liquid placebo given 1 and 3 hr after meals and bedtime.

Table 3

Intragastric H^+ Activities Following Meals and at Night (mmol/L), mean ± SEM

Test Condition	Placebo	A7	C+A7	C+A4
Breakfast (9:00-12:00)	14.11 ± 1.20	$4.95 \pm 1.15^{*,\dagger}$	$1.11 \pm 0.28^{*}$	$4.00 \pm 0.85^{*}$
Lunch (13:00-16:00)	10.31 ± 1.46	$1.63 \pm 0.41^{*,\dagger}$	$1.07 \pm 0.44^{*}$	$1.79 \pm 0.41^{*,\dagger}$
Supper (18:00-21:00)	6.29 ± 0.49	$2.57 \pm 0.48^{*}$	$3.03 \pm 0.58^{*}$	$2.61 \pm 0.62^{*}$
Overnight (22:30-8:30)	15.83 ± 1.03	10.61 ± 2.16	$3.63 \pm 0.72^{*}$	$4.34 \pm 1.25^{*}$
24 Hour Period	12.40 ± 0.84	$5.45 \pm 0.91^{*,\dagger}$	$2.72 \pm 0.35^{*}$	$3.43 \pm 0.47^{*}$

* $p<0.05$, as compared to placebo
† $p<0.05$, as compared to C+A7

Table 4

INTEGRATED GASTRIN RESPONSES AFTER MEALS (pg/ml/min)

	Placebo	A7	C + A7	C + A4
Breakfast (8:30-12:30)	2514 ± 496	4894 ± 1612	7116 ± 1624	5687 ± 1888
Lunch (12:30-16:30)	3846 ± 777	4116 ± 1008	6103 ± 2502	6906 ± 1291
Supper (17:30-0:30)	6996 ± 792	13260 ± 3009	8813 ± 2304	5878 ± 1257

Table 5

Cimetidine Pharmacokinetic Parameters of
Each Individual Patient Treated With
Combination of Cimetidine and Antacid (C+A7,C+A4)

Patient	Cmax(μg/ml)		Tmax(hr.)		t ½ (hr.)		AUC 0-∞ (μg.hr/ml)		AUC_{0-24} (μg.hr/ml)
	AM	PM	AM	PM	AM	PM	AM	PM	
C+A7									
1	4.2	1.7	1.5	2.0	3.54	*	22.12	*	*
2	3.0	2.1	3.0	2.0	2.98	5.83	15.52	16.35	32.30
3	6.6	2.5	1.0	2.0	3.11	3.69	28.30	17.20	46.85
4	3.2	0.7	1.0	4.0	3.18	3.40	12.86	4.00	17.77
5	4.1	1.3	2.0	2.0	3.62	*	13.70	*	*
6	2.4	1.5	2.0	6.0	2.80	2.52	12.63	11.31	23.94
7	2.6	1.5	2.0	2.0	2.28	3.94	12.88	9.86	22.74
8	4.3	1.8	2.0	4.0	2.05	3.81	14.32	12.38	26.10
Mean	3.8†	1.6	1.8	3.0	2.95	3.87	16.54	11.85	28.28
SEM	0.5	0.2	0.2	0.5	0.20	0.40	2.01	2.00	4.19
C+A4									
1	5.2	2.3	0.5	2.0	1.91	3.86	15.37	11.23	25.22
2	5.4	2.1	1.0	4.0	2.61	7.19	24.84	17.05	43.40
3	3.1	2.3	0	4.0	4.60	4.91	*	15.65	*
4	1.9	1.6	2.0	2.0	4.56	8.44	14.29	14.07	27.05
5	4.7	2.0	1.0	4.0	3.94	3.06	17.43	12.14	30.13
6	3.3	1.8	1.0	6.0	2.53	1.84	16.03	10.13	24.79
7	5.9	3.1	0.5	4.0	2.09	2.13	16.78	13.00	29.48
8	4.9	1.9	0.5	4.0	2.50	2.16	14.32	8.76	24.16
Mean	4.3	2.1	0.8	3.8	3.09	4.20	17.01†	12.75	29.18
SEM	0.5	0.2	0.2	0.5	0.39	0.87	1.38	0.98	2.52

*Values could not be determined because of insufficient data.
† $p<0.05$, compared to PM value.

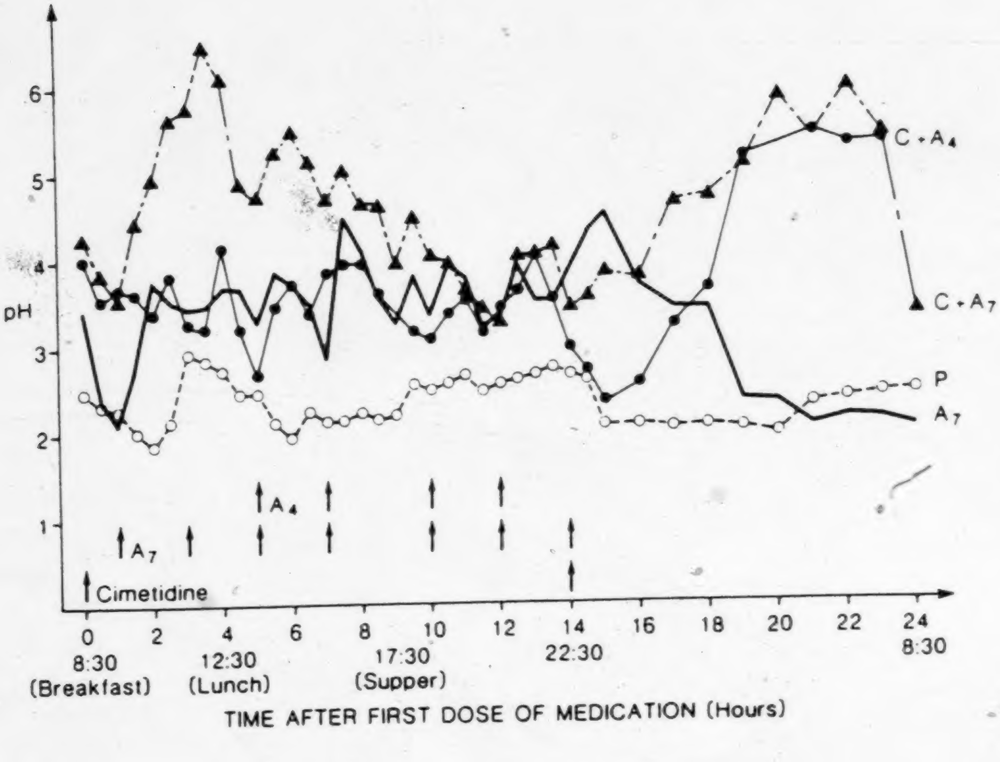

Figure 1. Mean intragastric pH over 24-hour period. Arrows indicate times at which medications are given.

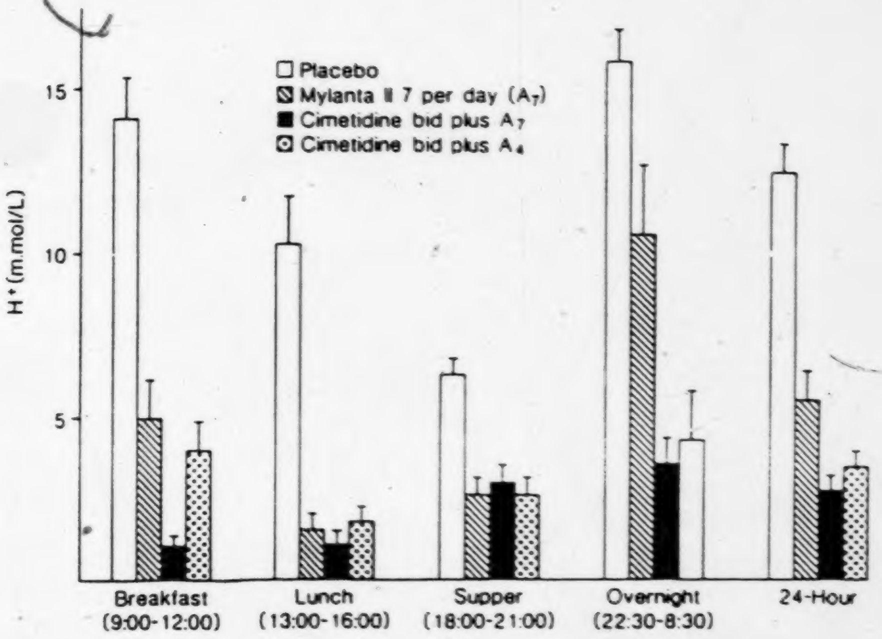

Figure 2. Mean H^+ activities after meals, overnight and over 24-hour period. Significant differences are indicated by *($p<0.05$).

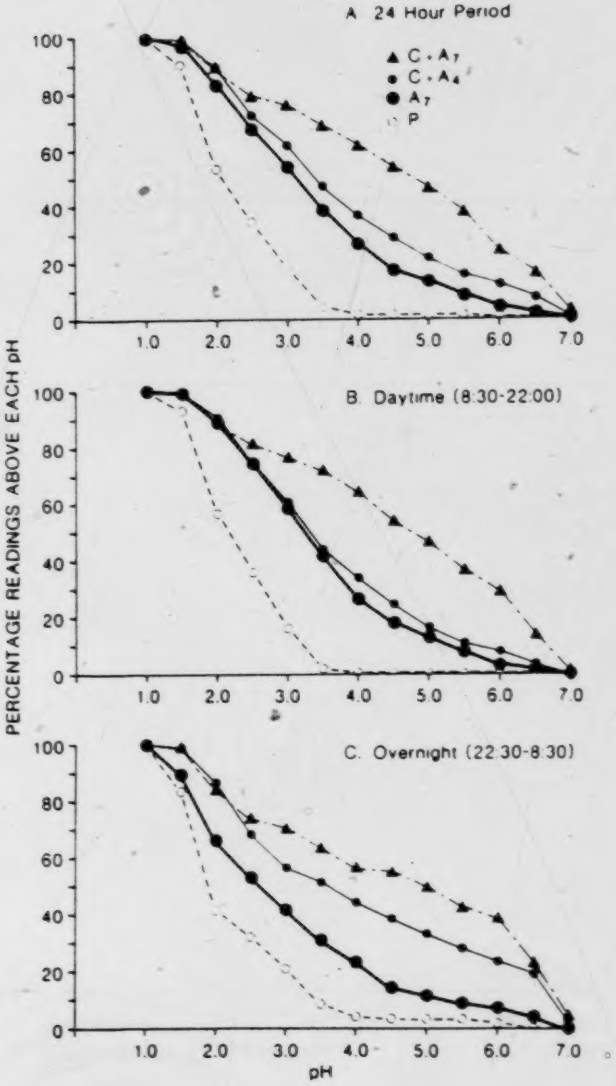

Figure 3. Cumulative percentage of pH readins at or above each pH value during A) 24-hour, B) daytime and C) overnight.

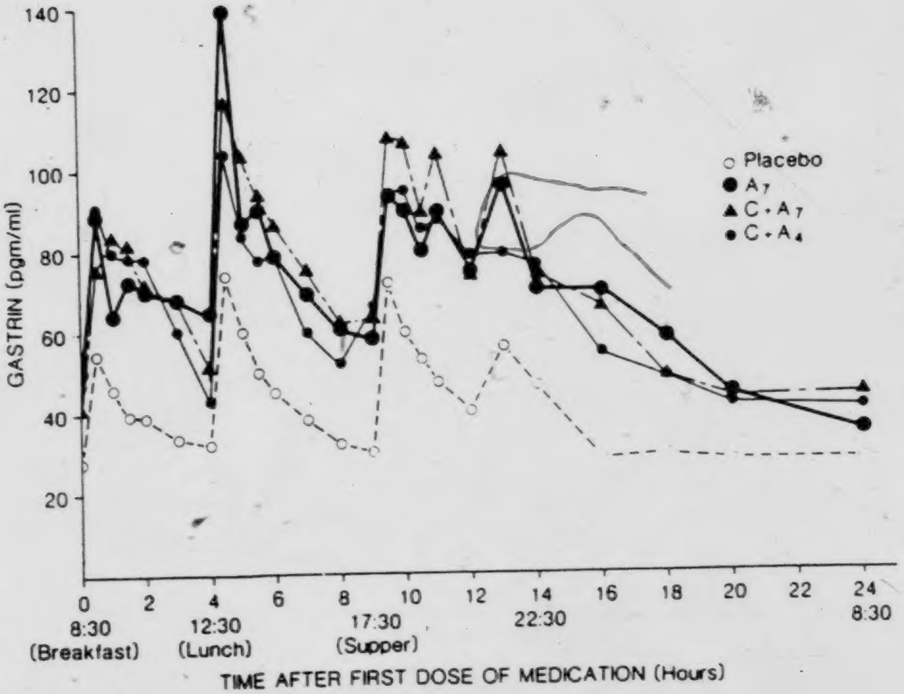

Figure 4. Mean serum gastrin concentration over 24-hour period (pg/ml).

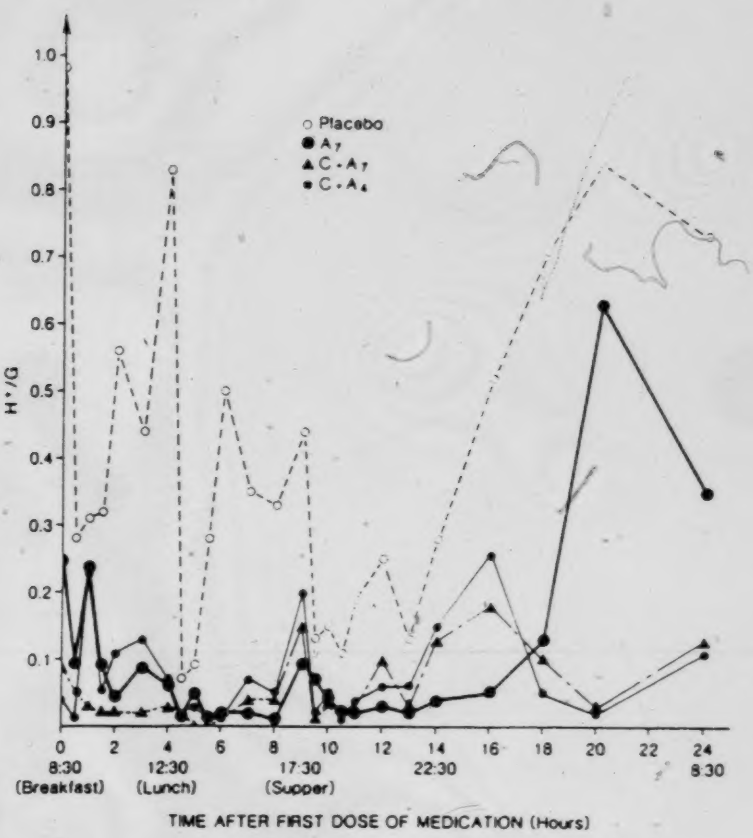

Figure 5. Ratio of intragastric H^+ and serum gastrin concentration (H^+/G) over 24-hour period.

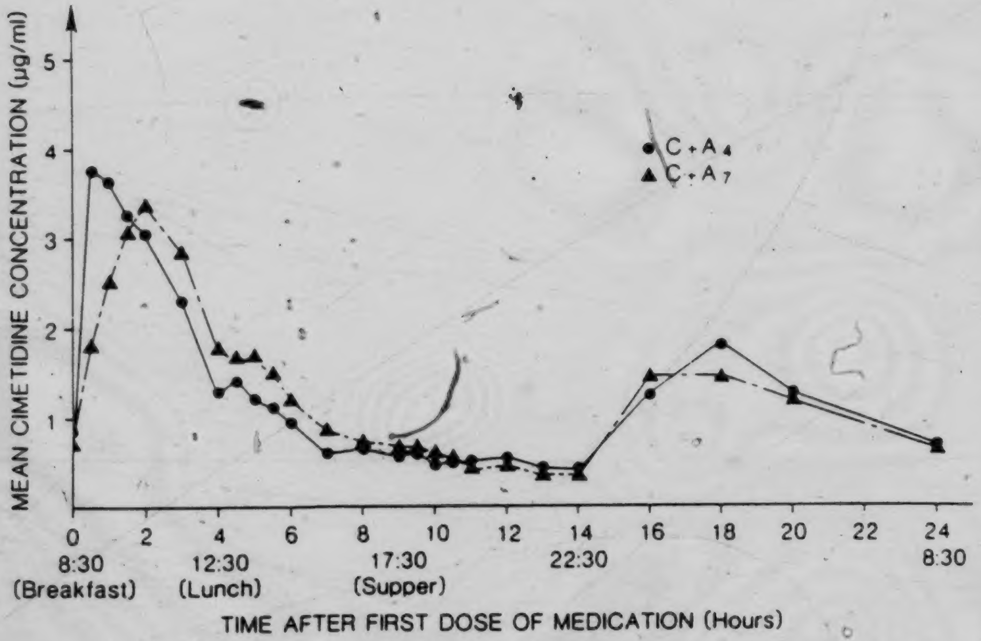

Figure 6. Mean plasma cimetidine concentration over 24-hour period.

5. COMPARISON OF CIMETIDINE AND RANITIDINE ON 24-HOUR INTRAGASTRIC ACIDITY AND SERUM GASTRIN PROFILE IN PATIENTS WITH ESOPHAGITIS

[A modified version of this chapter has been submitted to Digestive Diseases and Sciences, 1984 (in press). V. Mahachai, K. Walker, A.B.R. Thomson.]

SUMMARY

Twenty-four hour intragastric pH and serum gastrin profiles were monitored in six male asymptomatic patients who previously were found to have esophagitis on endoscopy and biopsy. They received cimetidine 300 mg qid (C), ranitidine 150 mg bid (R), or placebo (P) for one week each, utilizing the Latin Square Design. The mean BAO was 0.4 ± 0.2 mmol/hr, and the pentagastrin-stimulated MAO was 21.2 ± 3.2 mmol/hr. In the P-treated patients, the pH fluctuated between 1.8 - 3.5 and over 90% of the readings were less than pH 4. As compared to P, both C and R significantly suppressed H^+ after breakfast, overnight, and over the 24-hour period. The mean pH after lunch was significantly higher in R than in P, but not in C. Over the 24-hour period, a higher percentage of the readings were above pH 4.0 in R as compared to C. During the night 50% of the pH readings were above pH 4.0 in C and R, whereas in P 50% of the pH readings were less than pH 2.0. The integrated gastrin responses after each meal were similar in C and R and were greater than in P. The biphasic response of the ratio of H^+ and gastrin (H^+/G) following each meal was suppressed by both H_2-receptor antagonists, with numerically lower values obtained in R than in C. This study suggests that ranitidine 150 mg bid is superior to cimetidine 300 mg qid in suppressing the 24-hour intragastric acidity.

INTRODUCTION

The abnormalities of competency of the lower esophageal sphincter, the clearing capacity of the esophagus, and normal gastric emptying are considered to be important mechanical factors in the pathogenesis of gastroesophageal reflux disease. However, gastroesophageal reflux has been shown to occur in healthy controls without producing esophagitis[1]. It has been shown that patients with reflux esophagitis have increased frequency and duration of reflux episodes as compared to healthy controls[1]. A recent study showed that the basal acid output (BAO) as well as both the basal and maximal secretory volume in response to pentagastrin were increased in patients with gastroesophageal reflux disease as compared with healthy controls[2]. While the gastrin response to food is apparently normal in gastroesophageal reflux disease, the basal gastrin concentration may be elevated[3].

Both ranitidine and cimetidine are effective in the reduction of gastric acidity but ranitidine may be more potent[4]. Accordingly, this study was undertaken to compare the effect of ranitidine and cimetidine on 24-hour intragastric pH and serum gastrin profile in six currently asymptomatic patients with previously documented esophagitis.

METHODS

This study was a double-blind repeated measures Latin Square design in which each subject received all possible treatments: ranitidine 150 mg twice a day (8:30 and 17:30 hr), cimetidine 300 mg four times daily (8:30, 12:30, 17:30, and 22:30 hr), and matching placebo in a sequential random order. Each treatment was administered for one week with the acid secretion studies and gastrin analyses carried out on the last day of the treatment week. Six patients with currently asymptomatic gastroesophageal reflux disease were studied. All of these patients had previously documented esophagitis on endoscopy and biopsy. They became asymptomatic after a 6-12 week course of ranitidine or antacids, and have since remained well with only mild and infrequent symptoms of gastroesophageal reflux. None of the patients were receiving treatment for gastroesophageal reflux disease at the time of entry to the study. All patients were male with an average age of 52.8 yrs (range 32-66 yrs). The patients were free of significant systemic disease, and had no previous gastric or esophageal surgery. Before entry into the study, all patients had a pentagastrin test (6μg/kg subcutaneously). The mean basal acid output (BAO) was 0.4 ± 0.2 (mean ± SEM) mEq/hr, with a range of 0 - 1.4 mEq/hr. In response to pentagastrin, the mean maximal acid output (MAO) was 21.2 ± 3.2 mEq/hr, with a range of 9.2 - 30.8 mEq/hr. These values were considered to be normal, but two subjects had MAO of 30.0 and 30.8 mEq/hr. The project was approved by the Ethics Committee of the Department of Medicine, University of Alberta, and informed consent was obtained from each patient.

On the study day (day 7, 14 or 21), the patients were admitted to a specially allocated hospital ward at 7:00 hr following a 12 hour overnight fast. Water was taken ad libitum during the fast until the start of the gastric acid secretion study. A strict protocol was followed: a nasogastric tube was first positioned under fluoroscopic control so that the tip was in the most dependent part of the stomach. Immediately after fluoroscopy, an intravenous infusion of 0.9% saline was initiated at a rate sufficient to keep the vein open to allow free access to sampling of venous blood. At 8:30 hr, patients received a standard meal (Table 1), and their first dose of drug or identical placebo. Additional doses of drug or placebo were given at predetermined times.

Gastric acidity was monitored by a method similar to that described by Pounder et al[5]: five ml samples of gastric contents were aspirated every 30 minutes while the patient was awake, and at 60 minute intervals during the sleeping hours. If necessary, a 5 ml flush of 0.9% saline was used to obtain sufficient gastric fluid for pH measurement and to wash the syringe used to aspirate the gastric juice. The pH of the sample was measured to the nearest 0.10 unit using a combined glass and reference electrodes and pH meter (Canlab 130) which had been calibrated with standard buffers (pH 2.0 and 4.0) before each batch of measurements. The aspirate was then returned to the stomach contents to ensure complete absorption of medications. Blood samples were drawn every 30 minutes while the patient was awake and every two hours during the night. Blood samples were centrifuged and the serum was immediately separated and stored at -4°C for further determination of gastrin concentration.

All subjective symptoms observed during the study period were recorded and vital signs were monitored. At the end of the 24-hour study periods, the intravenous line and nasogastric tube were removed, and patients were instructed on the medications to be taken over the following week.

The standardized meals with identical composition of carbohydrate, fat, protein and volume were provided to the patients in hospital similar to our previous study[6]. Regular snacks of known composition were allowed between meals. Only decaffeinated coffee was permitted and cigarette consumption was discouraged, but if the patient smoked then the number of cigarettes was recorded. The subjects were ambulant and were encouraged to entertain themselves on the ward. The patients consumed an average of 1798 ± 29 kcal/day (range 1662 - 2029 kcal/day), comprised an average of 218 gm carbohydrate, 82 gm protein and 65 gm fat. The proportions of the total calories provided by carbohydrate, protein and fat were 49%, 18%, and 33% respectively. There was no difference in these proportions of food intake between the three trial periods. The average fluid intake per day was 2.43 L, and subjects smoked an average of 10 cigarettes per day.

The intragastric hydrogen activities (H^+) were converted from the pH values using a standard table[7]. The values of H^+ were compared over a 90 minute period after each meal, as well as overnight (22:30 - 8:30) and for the total 24 hour period. The pH profiles of all treatment groups were also compared by deriving the cumulative percentage of pH readings at or above each pH value ranging from 1.0 - 7.0.

The serum gastrin concentration was determined by a radioimmunoassay method using a commercial kit (Schwarz-Mann). The antibody employed has similar affinities for G-34 and G-17 molecular forms. The integrated gastrin response after each meal was calculated by using the trapezoidal rule to obtain the area under the concentration-time curve (AUC) from time zero (i.e. time of a meal) to a certain time point after each meal where the gastrin concentration approached its basal value. The basal concentration, present at mealtime, was taken into account by calculating the AUC from this point to the same time point, and subtracting it from the overall AUC after each meal. The ratios of H^+ and serum gastrin concentration over a 24 hour period were compared between each treatment group, and the correlation of H^+ and gastrin concentration were studied in all groups.

STATISTICAL ANALYSIS

The Student's t-distribution test was used for statistical analyses of the pH values and intragastric H^+ in all treatment groups. The p values of < 0.05 were considered significant. The frequency distribution of the pH readings at or above 4.0 in each group was studied using chi-square analysis. A repeated measures analysis of variance and covariance test was applied to see if there was an overall difference of the changes on serum gastrin profile, area under the curve, and ratio of H^+ over gastrin between the treatment groups at each of the defined periods. A least square difference test was applied only if there was an overall significant difference.

RESULTS

A. Intragastric pH profile

The 24-hour intragastric pH profiles of the six patients with gastroesophageal reflux disease are shown in Figure 1. In patients treated with placebo, the pH ranged from 1.8 - 3.5. In contrast, in patients treated with an H_2-receptor antagonist, the intragastric pH values were higher.

In the placebo groups, 50% of the pH readings were below a pH of

2.3 during the 24-hour period, during the daytime and during the nighttime (Figure 2). In patients given cimetidine 300 mg qid, 50% of the pH readings were above 3.7 during the 24-hour period, during the daytime and overnight. Following ranitidine 150 mg bid, 50% of the readings were above 4.6 during each of these intervals. These differences between the placebo and the H_2-receptor antagonist groups were significant at each time period ($p<0.05$). Using human hemoglobin as a substrate, proteolytic activity of gastric juice is markedly decreased at pH 4.0[8]. During the 24 hour period (Figure 2A), the percentage of readings at or above pH 4.0 was significantly higher in the ranitidine than in the placebo group ($p \leq 0.05$), or in the cimetidine than in the placebo groups ($p<0.05$, 60%, 40% and 10% respectively). Similarly, a significantly greater percentage of the readings was at or above 4 in the ranitidine- and cimetidine-treated patients than in the placebo group when measured during the daytime (Figure 2B) or during the nighttime (Figure 2C). The percentage of pH readings above 4.0 was greater in the ranitidine than in the cimetidine group for the 24-hour period and during the daytime ($p<0.05$).

With either cimetidine or ranitidine, the intragastric H^+ activity at each time period was less than that observed in the placebo group (Figure 3). The difference in the mean H^+ activity in the placebo and in the cimetidine groups was statistically significant after breakfast, overnight, and for the 24-hour period (Table 2). The difference in the mean H^+ activity in the placebo and in the ranitidine group was statistically significant after breakfast, after lunch, as well as overnight and over the 24-hour period. Although the difference in the H^+ activity in the cimetidine and in the ranitidine groups failed to achieve statistical significance ($p>0.05$), the mean H^+ activity after lunch was significantly lower than placebo in the ranitidine ($p<0.025$) but not in the cimetidine group (Table 2).

B. Serum Gastrin Concentration

After an overnight fast, the mean basal gastrin concentration (Figure 4) was similar in patients treated with placebo, ranitidine and cimetidine (46.2, 56.0 and 53.3 pg/ml). The serum gastrin concentration increased after each meal to reach a peak at about one hour. In the placebo group, the serum gastrin concentration returned to the basal level within 4 hours after breakfast and after lunch, whereas the gastrin concentration remained at least 25% above the basal value after breakfast and after lunch in patients given cimetidine or ranitidine. After supper, a biphasic gastrin response was noted, with an initial peak at 1 hour and a later peak at 4 hours, shortly after the bedtime snack. This biphasic response was seen in the three treatment groups and it was not until 9 hours after supper that the plasma gastrin concentration returned to the basal level after supper in the cimetidine and ranitidine groups. In the placebo group, the serum gastrin concentration increased to approximately 112% of the basal value following each meal, whereas the postprandial gastrin concentration increased more rapidly and higher to approximately 167% of the basal value in the patients receiving one of the H_2-receptor antagonists. However, there was no significant difference in the overall increase of serum gastrin concentration after meals in all treatment groups.

The integrated gastrin response (IGR) was calculated for a 2 hour period following each meal. In the placebo group (Table 3), there was no statistically significant difference between the mean values of the IGR after breakfast (3040 ± 679 pgm.min/ml), after lunch (5115 ± 650 pgm.min/ml), and after supper (3595 ± 860 pgm.min/ml). Since the food-stimulated gastrin concentration had not returned to the basal value until 4 hr after breakfast and lunch, and until 9 hr after supper in the cimetidine and ranitidine groups (Figure 4), the IGR was also calculated for longer intervals (Table 3). The difference of 4 hr IGR following breakfast and lunch in the placebo group failed to show statistical significance.

In the patients given cimetidine, the two hr IGR was higher after breakfast, lunch and supper as compared to the placebo group (Table 3), but this difference was not statistically significant. Similarly, the 4 hr IGR after breakfast and lunch and the 7 hr IGR after supper were higher in the cimetidine than in the placebo group, but the significant difference between groups was obtained only with the 7 hr IGR after supper ($p < 0.01$). The IGR at the different time intervals was also higher in the ranitidine than in the placebo group, but there was no difference in the food-stimulated gastrin response in the cimetidine versus the ranitidine groups.

C. Relationship between H^+ and Gastrin Concentration

In the placebo-treated patients, the ratio of H^+ to serum gastrin concentration (H^+/G) increased dramatically after each meal (Figure 5). In contrast, only a modest change in the ratio of H^+/G was observed in the cimetidine-treated patients following meals. In the ranitidine-treated patients, this ratio remained essentially constant over the 24 hour period. The differences in the ratio H^+/G after each meal were significant between the placebo and cimetidine or ranitidine.

In the placebo-treated patients, there was a weak negative correlation between serum gastrin concentration and H^+ ($r=-0.19$, $p<0.05$). Such a relationship was observed neither in the cimetidine group ($r=0.05$) nor in the ranitidine group ($r=0.13$).

DISCUSSION

In placebo-treated patients with a past history of endoscopically and biopsy proven esophagitis, the intragastric pH ranged between 1.8 - 3.5 (Figure 1) and over a 24-hour period, less than 10% of the pH readings were above 4.0 (Figure 2A). Therefore, the intragastric fluid which was available for regurgitation into the esophagus was highly acidic and potentially damaging to this organ. The administration of H_2-receptor antagonists was associated with a marked reduction in intragastric H^+ after meals, overnight and over the 24-hour period (Figure 3). In addition, 50% of the intragastric pH readings were pH 3.7 or greater in the cimetidine- and ranitidine-treated groups. This compared with pH 2.3 for the placebo-treated patients at all time periods (Figure 2). Also, a higher percentage of the readings at pH 4 or above was obtained in the cimetidine- or ranitidine-treated patients as compared to placebo. Cimetidine and ranitidine have been shown to be useful in the management of GERD[9,10]. This study suggests that one likely mechanism of this beneficial effect of an H_2-receptor antagonist is the pronounced reduction in intragastric H^+ after meals and overnight.

Chemical and pharmacological differences exist between cimetidine and ranitidine[11]. Previous workers have established that 150 mg of ranitidine given twice daily was more effective than 1000 mg daily of cimetidine in the reduction of mean 24 hour hydrogen ion activity and nocturnal acid output when tested in ten male patients with endoscopically proven chronic duodenal ulcers in remission[4]. It should be noted that in this study using 300 mg ranitidine or 1200 mg cimetidine daily 1) intragastric H^+ was significantly suppressed after lunch in patients treated with ranitidine but not with cimetidine; 2) intragastric H^+ was numerically less in the ranitidine- than in the cimetidine-treated patients after breakfast, after lunch, and over a 24-hour period; 3) comparing ranitidine with cimetidine, the intragastric pH observed in half of the readings during the daytime, overnight and during the 24-hour period were higher (Figure 2) and 4) the percentage of readings above pH 4 was greater during the daytime and during the 24-hour period in the ranitidine- versus the cimetidine-treated patients ($p<0.05$). Thus ranitidine would appear to be superior to cimetidine in the suppression of intragastric acidity when tested in patients with chronic duodenal ulcer disease[4] or esophagitis.

The serum gastrin concentration required up to 4 hr to return to basal levels after the first two meals of the day (Figure 4). In patients given placebo, the gastrin response to supper was unusual in two ways: a biphasic response was observed, and the gastrin returned to the basal concentration only after 7 hr. This study does not establish the basis for the difference of responses following the third meal of the day, but this biphasic response following supper was also observed in patients treated with cimetidine and with ranitidine. In these cimetidine- and ranitidine-treated patients, the gastrin concentrations following supper remained above the basal level for an even more prolonged interval. As expected, food-stimulated gastrin concentration in the serum was higher in cimetidine- and ranitidine-treated patients (Figure 4). However, the correlation between H^+ and gastrin was weak in the placebo group ($r=-0.19$, $p<0.05$) and was non-significant in the cimetidine and in the ranitidine groups. If the reduction in H^+ was closely associated with changes in gastrin, then the ratio of H^+/gastrin would be unchanged between the placebo, cimetidine and ranitidine groups. This was not the case (Figure 5). This suggests that the H_2-receptor antagonist may have an effect on gastrin release which is not explained simply by the reduction in H^+. From this data, however, we are not able to specifically determine whether the H_2-receptor antagonists have an effect on the gastrin receptor, nor does our data allow comment on any possible effect of H_2-receptor antagonists on parietal cell sensitivity to food, or antral cell sensitivity to acid inhibition. However, in view of the previous observation of elevated fasting gastrin concentrations in some patients with GERD[3], and the elevated postprandial integrated gastrin responses in the cimetidine- and the ranitidine-treated patients (Table 3), the longterm effect of the H_2-receptor antagonists on gastrin metabolism in GERD must be assessed.

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Table 1: SAMPLE OF TYPICAL DAILY FOOD INTAKE

Time	Protein Meal	Fat (g)	CHO (g)	Fluid (g)	Energy (cc)	(kcal)
0830	Breakfast - toast/jam - cereal/milk - scrambled egg - juice - coffee/tea/water - cream/sugar	17.0	16.0	50.5	530	
1030	Morning Snack - cookies - coffee/tea/water - cream/sugar	1.5	3.0	20.0	380	
1230	Lunch - tossed salad/dressing - roast beef - mashed potato/butter - carrots - canned fruit - coffee/tea/water - cream/sugar	20.0	15.0	53.5	380	
1500	Afternoon Snack - cookies - coffee/tea/water - cream/sugar	2.0	6.0	31.0	380	
1730	Supper - soup - sandwich - fresh fruit - coffee/tea/water - cream/sugar	32.0	17.0	47.0	380	
2030	Bedtime Snack - cheese and crackers - coffee/tea/water - cream/sugar	9.5	8.0	16.0	380	
Total		82.0	65	218	2430	1785

Table 2: INTRAGASTRIC H^+ FOLLOWING MEALS, OVERNIGHT AND OVER 24-HOUR PEROID (mmol/L, Mean ± SEM).

Test Condition	Placebo	C-300 qid	R-150 bid
Breakfast (9:00-10:30)	7.76 ± 3.18	$0.77 \pm 0.22^{**}$	$0.20 \pm 0.09^{\dagger\dagger}$
Lunch (13:00-14:30)	3.35 ± 1.77	2.51 ± 1.31	$0.28 \pm 0.06^{\dagger\dagger}$
Supper (18:00-19:30)	5.17 ± 1.01	0.11 ± 0.02	0.59 ± 0.02
Overnight (22:30-8:30)	12.17 ± 1.02	$2.59 \pm 0.69^{*}$	$2.33 \pm 0.44^{\dagger}$
24-Hour Period	10.65 ± 1.01	$2.93 \pm 0.45^{*}$	$1.30 \pm 0.21^{\dagger\dagger}$

Placebo versus cimetidine; *, $p<0.05$; **, $p<0.025$

Placebo versus ranitidine; †, $p<0.05$; ††, $p<0.025$

Table 3: POSTPRANDIAL INTEGRATED GASTRIN RESPONSES OVER EACH MEAL

(pg.min/ml, Mean ± SEM)

Time Period	Placebo	Cimetidine	Ranitidine
Breakfast			
8:30 - 10:30 (2 hrs)	3040 ± 679	6373 ± 973	5178 ± 1041
8:30 - 12:30 (4 hrs)	4030 ± 1079	10738 ± 1647	10868 ± 2477
Lunch			
12:30 - 14:30 (2 hrs)	5115 ± 650	7043 ± 1820	7470 ± 1767
12:30 - 16:30 (4 hrs)	6920 ± 882	10693 ± 2395	11430 ± 2855
Supper			
17:30 - 19:30 (2 hrs)	3595 ± 860	8213 ± 1928	6873 ± 1477
17:30 - 0:30 (7 hrs)	10069 ± 2135	21742 ± 2816*	27713 ± 3201†

Placebo versus cimetidine; *, $p<0.05$.

Placebo versus ranitidine; †, $p<0.05$.

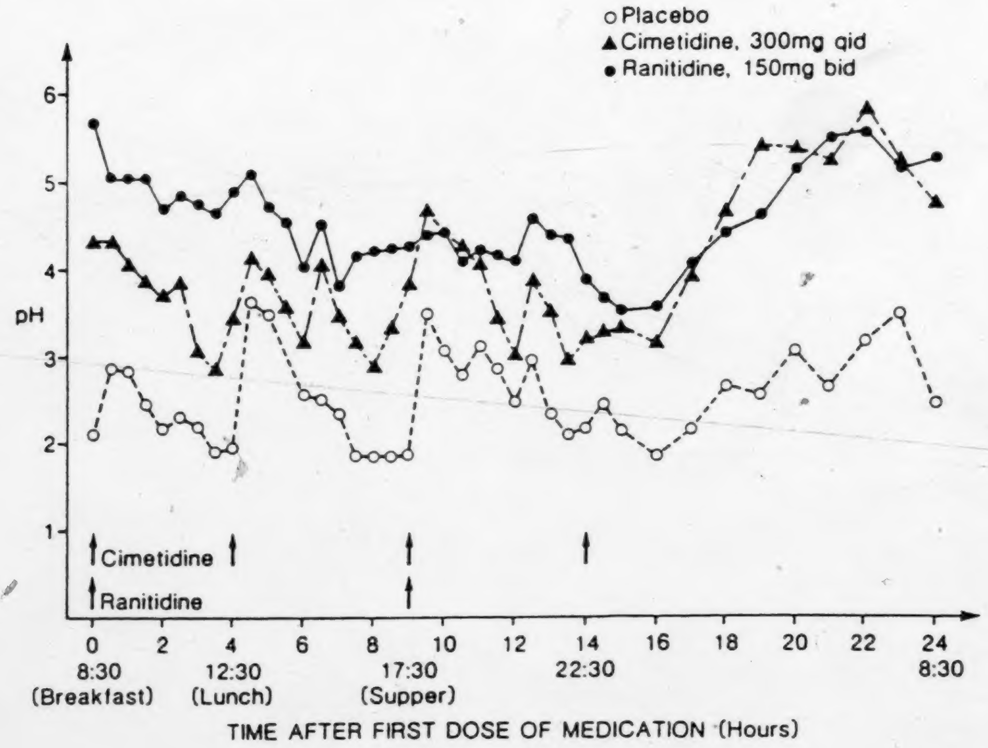

Figure 1. Intragastric pH Over 24 Hour Period. The patients were given cimetidine or ranitidine at the times indicated by the arrows.

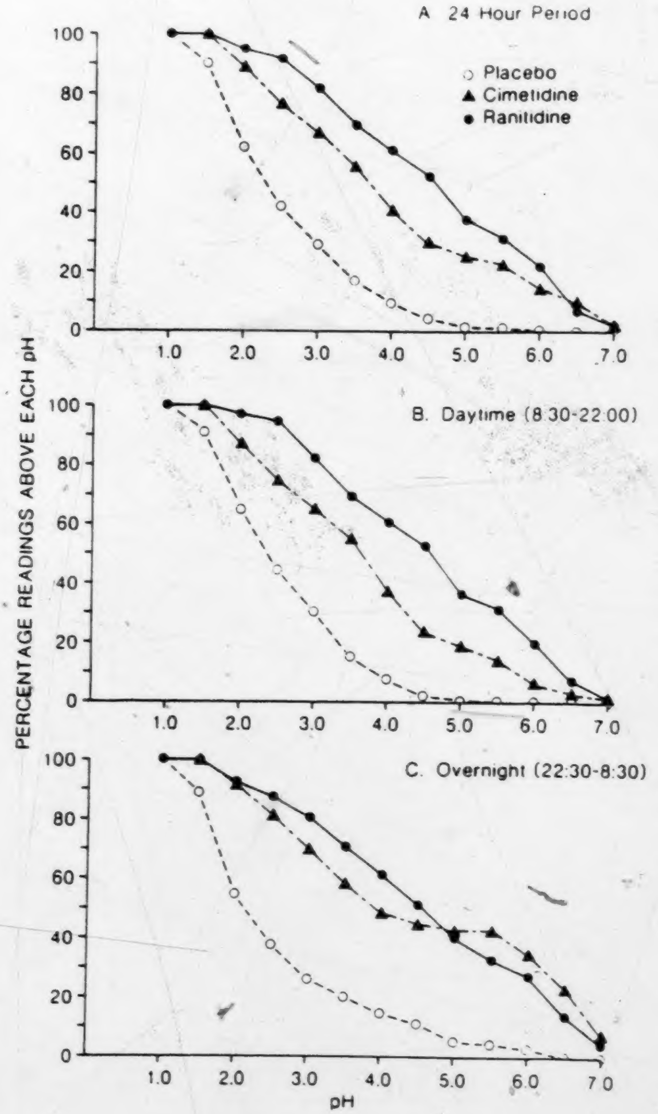

Figure 2. Cumulative percentage of the pH readings at pH values from 1.0 to 7.0 in all treatment groups during the (A) 24-hr period, (B) daytime and (C) overnight.

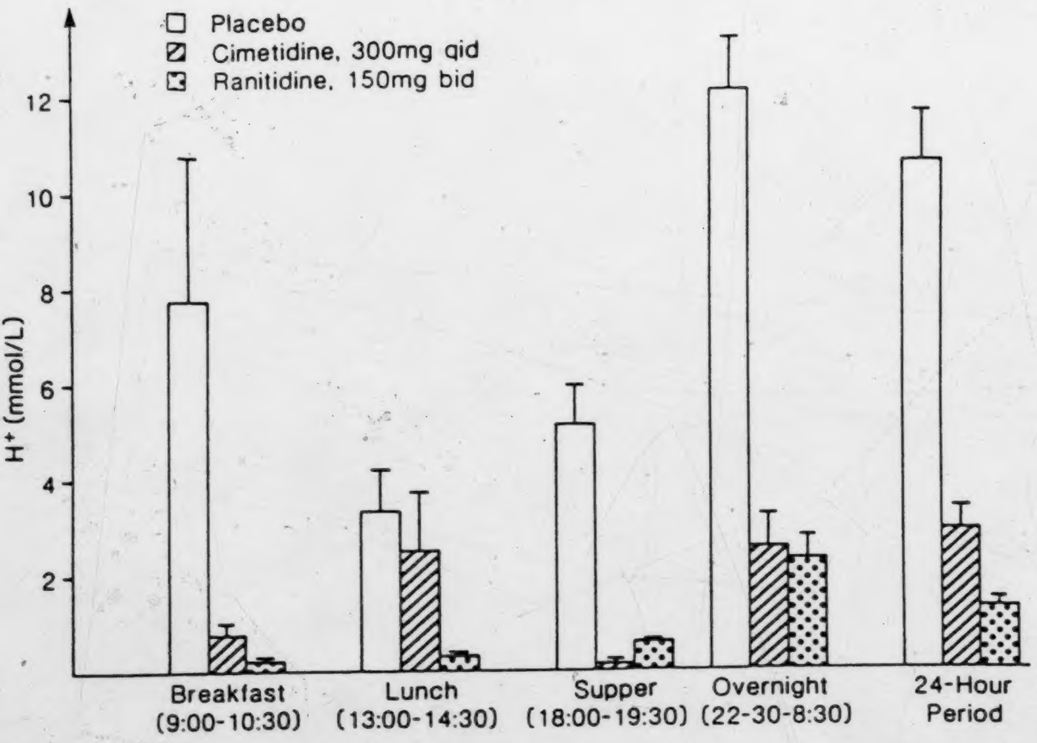

Figure 3. Intragastric H^+ Activities Following Meals, Overnight and Over 24-Hour Period.

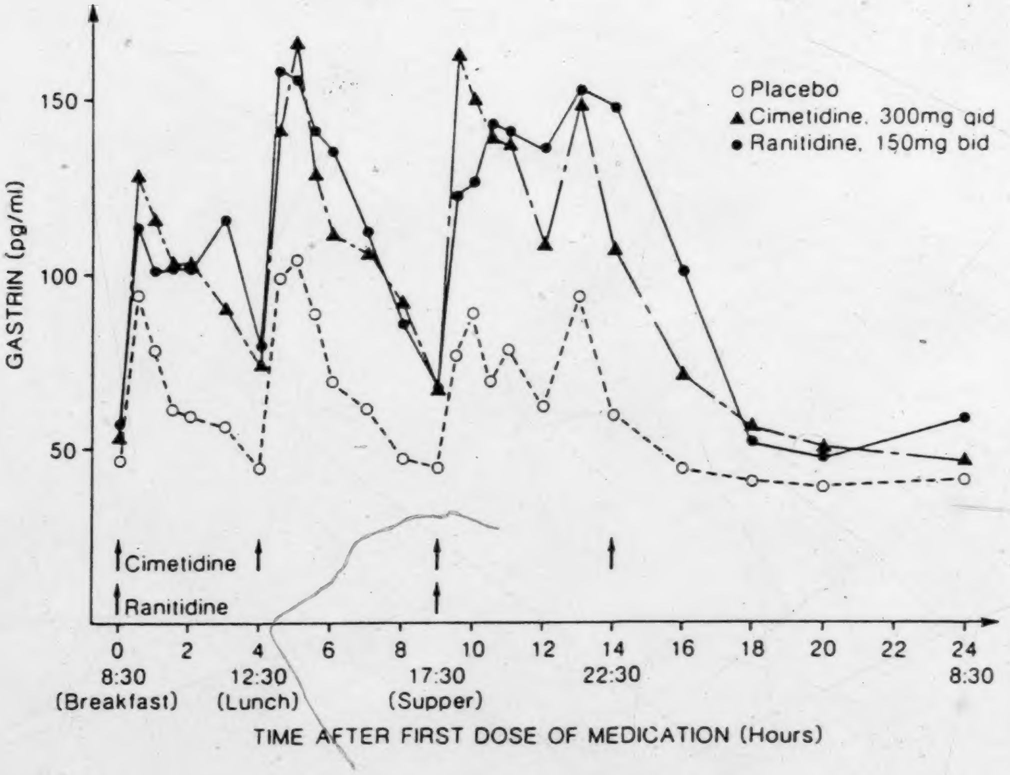

Figure 4. Serum Gastrin Concentration over 24-Hour Period. The patients were given cimetidine or ranitidine at the times indicated by the arrows.

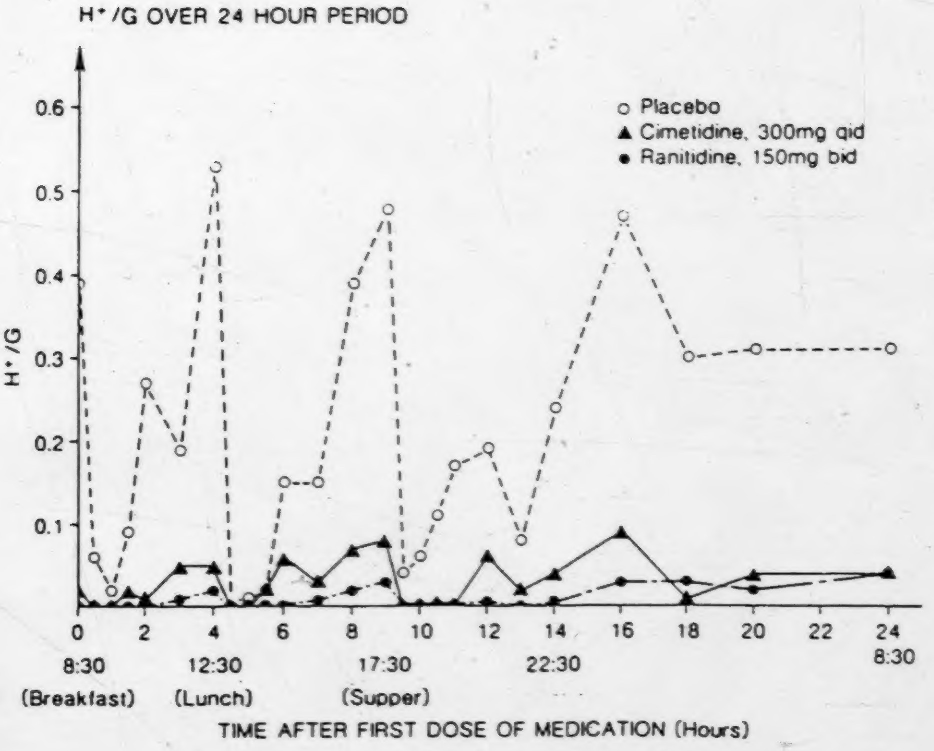

Figure 5. Ratio of Hydrogen Ion Concentration to Serum Gastrin Concentration Over 24-Hour Period.

6. COMPARATIVE EFFECTS OF PIRENZEPINE AND CIMETIDINE, ALONE AND IN COMBINATION, ON 24-HOUR GASTRIC ACIDITY IN DUODENAL ULCER DISEASE

SUMMARY

Both pirenzepine and cimetidine have been shown to be beneficial in the healing of duodenal ulcers (DU). The aim of this study was to determine the effects of pirenzepine 50 mg bid (PRZ), cimetidine 600 mg bid (C), either alone or in combination, on 24 hour intragastric acidity, nocturnal gastric secretory volume and acid output, and serum gastrin profile in DU. Eight asymptomatic patients with healed DU received placebo, PRZ, C, or C+PRZ for one week each in a sequential order. All measurements were carried out over 24 hour period on the last day of each treatment week. As compared with P, C was associated with lower hydrogen ion activities (H^+) following breakfast, during the night and over the 24 hour period. PRZ by itself failed to suppress H^+, but the combination of C+PRZ resulted in a more prolonged acid suppression with lower H^+ after lunch when compared to C alone. The effect of cimetidine on the suppression of nocturnal acid secretory volume and acid output could be further enhanced by addition of PRZ. The fasting serum gastrin concentrations were similar in all treatment groups excluding one patient with antral G cell hyperplasia; the postprandial gastrin responses were similarly higher in C and C+PRZ than in P. This study suggests that there is an added benefit of combination therapy of cimetidine and pirenzepine which may be useful in patients who fail to respond to single agent therapy.

INTRODUCTION

Pirenzepine is a selective antimuscarinic agent of high affinity to the gastric mucosa which decreases basal and stimulated gastic acid secretion while producing much less anticholinergic side effects as compared with conventional anticholinergics[1,2]. Gastric acid secretion in response to peptone and sham feeding was found to be inhibited by this agent[3,4]. Pirenzepine decreases pentagastrin-stimulated acid output by reducing the volume of acid, rather than by affecting the gastric acidity[1,5]. The beneficial effect of this agent in treating active duodenal ulcer has been suggested by previous studies[6,7]. A synergistic interaction has been demonstrated between pirenzepine and an H_2 receptor antagonist[8,9]. The combination certainly provides a potentially beneficial effect in the treatment of peptic ulcer disease. The present study was undertaken to establish the pharmacological effect of pirenzepine 50 mg bid and cimetidine 600 mg bid, either alone or in combination, on 24-hour intragastric pH, nocturnal acid secretory output and serum gastrin concentration in patients with chronic duodenal ulcer disease.

METHODOLOGY

The method has previously been published[10]. Briefly, a double-blind, repeated measures, Latin square design was used in which each subject received all possible treatment in a sequential random order. Each treatment was administered for one week with acid secretion study, and gastrin analyses being carried out on the last day of each of the treatment week. The medication regimens consisted of four groups: pirenzepine 50 mg bid, cimetidine 600 mg bid, combination of pirenzepine and cimetidine given twice a day, and a placebo control group. This study was approved by the Ethics Committee of the Department of Medicine at the University of Alberta and informed consent was obtained from each patient.

A total of eight patients with duodenal ulcer previously documented by endoscopy or barium meal x-ray were studied. The patients were asymptomatic at the time of study and were not receiving any active treatment for duodenal ulcer disease. There were 5 males and 3 females with the mean age of 43.3 years (range 29-63 years). The mean duration of their disease was 4.9 years. All of them were free of significant systemic disease and they had no past history of gastric surgery or vagotomy. Physical examination, routine laboratory tests (CBC, biochemical profiles, urinalysis) chest x-ray, and ECG of each patient were normal.

The mean basal acid output (BAO) was 1.9 ± 0.6 mmol/hr (range 1.3 - 3.0 mmol/hr). In response to pentagastrin (0.6 mcg/kg) given subcutaneously, the mean maximal acid output was 35.4 ± 15.8 mmol/hr (range 14.0 - 68.0 mmol/hr); only three out of eight patients had MAO higher than 35 mmol/hr.

On the study day (day 7, 14, 21 and 28), each patient was admitted to a specially allocated hospital ward at 07:00 hr following a 12 hour overnight fast. A strict protocol was then followed (Table 1): a nasogastric tube (size 14-16 Fr.) was positioned under fluoroscopy so that the tip was in the most dependent part of the stomach. An intravenous infusion of 0.9% saline was initiated at a rate sufficient to keep the vein open. This allowed free sampling of venous blood for determinations of serum gastrin concentration, and plasma levels of cimetidine and pirenzepine. The results of the plasma drug levels will be presented elsewhere. The patients were provided with standardized meals and regular snacks, similar to our previous study[10]. The first dose of drugs or placebo was given at 08:00 hr, 30 minutes before breakfast. The subsequent dose of drugs or placebo was administered at 21.00 hr, 30 minutes before bedtime snack.

Gastric acidity was monitored by a method similar to that described by Pounder et al[11]. The sampling of gastric juice was obtained every 30 minutes while the patient was awake and every 60 minutes while the patient was asleep. The pH of the gastric aspirates was measured to the nearest 0.10 unit using a combined glass and reference electrodes and pH meter. The pH electrode was calibrated with standard buffers of pH 2.0 and 4.0 before each batch of measurements and at the end of the 24 hour sampling period.

Between 24:00 hr and 08:00 hr, gastric juice was aspirated continuously by Gomco suction at -50 mmHg, supplemented by manual aspiration applied every 20 minutes with the patients in the supine position. The pH and volume of the nocturnal hourly fractions of gastric aspirates were measured immediatly and the samples were then stored at -4°C. Within 24 hr, the total acidity (H^+ concentration) of each sample was determined by automatic titration to pH 7.0 using NaOH (100 mmol/l). Acid output was calculated from the product of the volume times the acid concentration. At the time of gastric pH measurement, a 5 ml venous sample was drawn, centrifuged and separated, then stored at -4°C for determination of serum gastrin concentration by radioimmunoassay using Schwarz-Mann commercial kit. The antibodies employed have affinities for both G-34 and G-17.

All subjective symptoms and vital signs were recorded during the trial period. Biochemical and hematological profiles were monitored during the study period. Only one patient consistently experienced a minimal degree of blurred vision during both weeks when pirenzepine was given either alone or in combination with cimetidine. Dry mouth was observed in two subjects, but only during one out of the two weeks that they were on pirenzepine.

The data of one patient was excluded from analysis. This patient had a high basal gastrin concentration and markedly increased gastrin concentration after meals, with an average peak of 1040 pgm/ml. In this patient, the gastrin concentration did not increase with secretin stimulation. The BAO and PAO of this patient were 0.9 and 14.0 mmol/hr, respectively. Immunocytochemical staining on antral or duodenal biopsies was not obtained, but it was presumed that this patient had antral G-cell hyperplasia.

STATISTICAL ANALYSIS

Descriptive statistics and differences among treatment groups and times were analyzed. An analysis of variance, with repeated measures on both drug and time was the major analytical procedure. The difference among treatment groups were tested by paired t-tests or non-parametric statistics, when necessary. The p value less than 0.05 was considered to be statistically significant.

RESULTS

Intragastric pH Profiles and Hydrogen Ion Activities

The 24-hour intragastric pH values of all treatment groups are shown in Figure 1. In placebo treated patients, the pH range between 1.5 - 3.3 over the 24-hour period, with fluctuations occurring after meals and during the night. In patients treated with pirenzepine 50 mg bid, the intragastric pH profile was similar to that observed in patients treated with placebo. Cimetidine given 600 mg bid resulted in higher intragastric pH values following breakfast and during the night, as compared to placebo. When combining pirenzepine with cimetidine, the higher pH values were again observed after breakfast and during the night as compared to placebo.

There were significant differences of the mean pH values over the 24-hour period among all treatment groups ($p<0.05$). Cimetidine, either alone or in combination with pirenzepine, resulted in higher mean pH values over the 24-hour period as compared to pirenzepine alone or placebo ($p<0.05$). Although the mean 24 hour pH value was numerically higher in the combination-treated group than in the cimetidine-treated group, (3.39 ± 1.00 versus 3.14 ± 0.89), the difference failed to reach statistical significance ($p>0.05$). Neither were the differences of the pH values between the pirenzepine-treated group and the placebo-treated group significant.

The mean values for the intragastric hydrogen ion activities were calculated over the time period after each meal, during the night and over the 24 hour period (Figure 2). When compared to placebo, pirenzepine by itself did not produce suppression of intragastric H^+ at any time period. Cimetidine significantly suppressed intragastric H^+ after breakfast, during the night, and over the 24-hour period ($p<0.05$). When combining pirenzepine to cimetidine, significant H^+ suppression was obtained following breakfast, lunch, overnight, and over the 24-hour period ($p<0.05$). The mean H^+ activities after breakfast and lunch were numerically lower in the combination group than in the cimetidine group but only the difference after lunch was significant ($p<0.05$).

As peptic activity is markedly decreased at pH 4.0[12], the relative frequency of pH readings > 4.0 were compared. The cumulative percentages of pH readings at or above each pH from 1.0-7.0 for all treatment groups are shown in Figure 3. During the daytime, higher percentages of the pH readings >4.0 were obtained in the cimetidine and in the combination-treated groups (18%), as compared to the placebo-treated group (5%). There was no difference in the percentages of the pH readings at or above 4.0 between the pirenzepine and placebo groups (Figure 3a). During the night, the combination regimen resulted in a higher percentage of the pH readings >4.0 as compared to the cimetidine group, which in turn yielded a higher percentage of pH readings >4.0 as compared to the pirenzepine or the placebo group (Figure 3b). However, the difference between the values in the combination- and cimetidine-treated groups was not significant. During the 24-hour period, higher percentages of pH >4.0 were observed in the cimetidine-treated group and in the cimetidine plus pirenzepine-treated group as compared to the placebo- or the pirenzepine-treated group (Figure 3c).

Nocturnal Acid Secretion

Cimetidine resulted in a numerical reduction of the nocturnal secretory volume and acid concentration from 01:00 to 05:00 hr, as compared to placebo, although the differences failed to reach significant levels (Figure 4,5). However, acid output was significantly suppressed by cimetidine during this time period ($p<0.05$, Figure 6). Pirenzepine by itself did not have any effect on nocturnal gastric volume, acid concentration, or acid output. However, when pirenzepine was combined with cimetidine, a significant suppression of nocturnal volume ($p<0.05$) and of nocturnal acid concentration and acid output ($p<0.01$) were obtained (Figures 4,5,6).

During the last hour of sleep (05:00 - 08:00 hr), the total acid output at each hourly interval was numerically lower in the combination treated group than in the cimetidine-treated group but the difference was not significant. The mean hourly volume, acid concentration and acid output overnight were suppressed by combination therapy (Figure 7). The overnight acid concentration and acid output were significantly lower in the cimetidine group than the values in the placebo group. The difference in the overnight acid volume between the cimetidine and placebo groups was not significant (Figure 7).

Serum Gastrin Concentration

In the placebo-treated patients, the serum gastrin concentration rose approximately 192% after each meal. The peak gastrin concentration occurred about 1 hour after each meal (Figure 8). The sustained increase in serum gastrin concentration was obtained only after suppertime, with a second peak of serum gastrin concentration occurring after the nighttime snack. This gastrin response after supper was more prolonged than after the first two meals of the day i.e. it took approximately 7 hours to return to the basal value.

Serum gastrin profiles were similar in the pirenzepine and placebo-treated groups. A higher peak serum gastrin concentration and higher gastrin response were obtained after each meal in the cimetidine- and in the combination-treated groups, as compared to the placebo group. Only the differences after breakfast were significant ($p<0.05$).

One patient was suspected of having antral-G cell hyperplasia, i.e. a high basal gastrin concentration with a markedly increased serum gastrin response after each meal. The fasting serum gastrin concentration failed to increase with secretin stimulation. The gastrin concentration profiles were similar after all treatment regimens and placebo in this patient with suspected antral G-cell hyperplasia.

When the values of the gastrin concentrations of this patient were excluded from the analysis, higher gastrin responses were again obtained after each meal in the cimetidine and combination treated groups as compared to the placebo group. In these two treatment groups, the gastrin concentration did not return to its basal values between the meals, and longer time was required for the gastrin concentrations to reach their basal values after suppertime.

The ratio of H^+ activities over serum gastrin concentration (H^+:G) was plotted over 24 hour period for all treatment groups. These values fluctuated markedly after each meal in the placebo-treated group (Figure

9). The ratio was suppressed throughout the 24-hour period in the cimetidine-treated group and the combination-treated group. The difference of H^+:G values between the pirenzepine-treated group was not significantly different than the placebo-treated group.

DISCUSSION

The usefulness of conventional anticholinergic agents in the treatment of peptic ulcer disease has been limited by the undesirable side effects such as dry mouth, blurred vision, tachycardia, and atony of urinary bladder and gastrointestinal tract. Gastric acid secretion in response to food is inhibited only by a maximum of 35% with a maximum tolerated dose of a conventional anticholinergic[13]. Pirenzepine is a selective antimuscarinic agent which distinguishes between different subclasses of muscarinic receptors[14], which has been proven to be beneficial in the treatment of peptic ulcer disease[15]. Although other antimuscarinic agents may have higher affinity for binding to parietal cell receptors than pirenzepine, they are not as selective as pirenzepine[16]. In the present study, pirenzepine 50 mg bid by itself did not have any effect on intragastric pH values over the 24-hour period (Figure 1). When acid secretion was measured overnight, pirenzepine failed to suppress the nocturnal acid volume, acid concentration or total acid output (Figures 4,5,6), whereas cimetidine did reduce intragastric H^+ activities, nocturnal acid secretory volume and total acid output. The effect of cimetidine 600mg bid was observed only after breakfast and during the night. When pirenzepine was combined with cimetidine, the acid inhibitory effect was observed for a more prolonged period, as H^+ activities were suppressed after lunch, in addition to being suppressed after breakfast and during the night. Nocturnal acid volume, acid concentration and acid output were suppressed by both cimetidine and by the combination of cimetidine and pirenzepine. Furthermore, the effect of combination therapy persisted for a longer period than cimetidine alone.

None of the treatment regimens had an effect on pH values after suppertime. This lack of suppertime effect of cimetidine on intragastric pH was similar to our previous observations where cimetidine was given either as 300 mg qid or as 600 mg bid[10]. The explanation for this confirmed observation is unclear. Intragastric H^+ activities tend to be lower after suppertime, with the higher values after breakfast and during the night. This diurnal variation of H^+ activities may be related to the buffering capacities of different meals of the day and the absence of food during the night. The gastrin response to meal is prolonged and sustained after suppertime, which again may be related to the size of the meal ingested at that time. This prolonged gastrin response after supper may provide the sustained stimulation of gastric acidity which makes it resistant to suppression by any of the treatment regimens employed in this study.

The effects of antimuscarinic agents on gastrin release in response to sham feeding and to meals have been reported. Vagal-mediated gastrin release may be enhanced by antimuscarinic agents like atropine, suggesting that this cholinergic input is predominantly inhibitory[17]. However, food-stimulated gastrin release is either unchanged or is inhibited by anticholinergic agents[18]. Pirenzepine does not affect vagal-mediated gastrin release[19] and it may decrease food-stimulated gastrin release when the pirenzepine is given in a high dose[20].

In this study, pirenzepine 50 mg given twice daily failed to affect the serum gastrin concentration in response to meals. It is not surprising that the gastrin responses to food were greatly enhanced by cimetidine, as gastrin release is partially under negative feedback control of gastric acidity[21]. However, the gastrin concentration is not closely related to H^+ activities: the ratio of H^+ activities to gastrin concentrations (H^+:G) markedly fluctuated in the placebo group and was suppressed in the cimetidine-treated group (Figure 9). This suggests that gastric acidity is under the influence of other factors beside gastrin, that the gastrin concentration is influenced by factors other than or in addition to intragastric pH, and that the sensitivity of acid stimulation by gastrin is suppressed by cimetidine. When combination of pirenzepine 50 mg bid and cimetidine 600 mg bid was used, the gastrin response to meals was also enhanced. Thus, there appears to be no further interaction between the cholinergic and the H_2-receptors on mediating the ratio of H^+:G.

Although previous studies have shown that pirenzepine decreased acid secretory response to pentagastrin by decreasing volume rather than acid concentration[1,5], nocturnal acid secretion in terms of volume, concentration and total acid output were not altered by pirenzepine in this study. The reasons for this lack of effect in this study are unclear. The volume measurement during the 24 hour period is not possible with this technique which measures pharmacological effect of treatment regimens on gastric acidity under physiologic conditions in responses to meals without manipulating the normal gastric physiology on the control of acid secretion. Gastric contents were aspirated for volume measurement and extragastric titration performed during the sleep hours when the acid secretion is free of stimulation from food. Potentiation of various secretagogues has been demonstrated with parietal cells in vitro[22]. Pirenzepine potentiates the antisecretory effect of cimetidine when the combination therapy is used. It is unlikely that this antimuscarinic agent provides further acid suppression by inhibiting vagal-mediated acid secretion or inhibiting gastrin release as pirenzepine by itself failed to suppress nocturnal gastric acid volume, acid concentration and total acid output. Furthermore, serum gastrin concentration was not altered by pirenzepine alone. It is possible that pirenzepine may prolong the effect of cimetidine by altering cimetidine bioavailabilities through its effect on gastric emptying. Pirenzepine has been shown to have higher affinity to gastric mucosa than to smooth muscle[16] thus gastric emptying would be affected to a lesser extent by this agent. The greater and more prolonged acid inhibition with combination of cimetidine and pirenzepine was not due to changes in the pharmacokinetics of cimetidine (unpublished observations). Both agents may act synergistically on receptor sites on parietal cells to inhibit gastric acid. This greater acid inhibition with combination of pirenzepine and an H_2-receptor has been shown to be useful in the treatment of gastric hypersecretory states[8], and may prove to be of benefit in the treatment of patients with duodenal ulcer disease, particularly in those patients in whom acid secretion is inadequately suppressed by a single agent, or in whom ulcers or ulcer symptoms fail to improve on single-agent therapy.

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Table 1: TRIAL PROCEDURE

SAMPLING TIME		PROCEDURE
07:00	admitted to metabolic ward, NG tube under fluoroscopy, IV infusion	
08:00	medication administered	
08:30	breakfast	
10:30	morning snack	gastric pH measurement every 30 min from 08:00-24:00. Serial blood sampling for gastrin concentration every 30 min after each meal.
12:30	lunch	
14:30	afternoon snack	
17:30	supper	
21:00	medication administered	
22:30	bedtime snack	
24:00	NG to Gomco sunction, supplemented by manual aspiration every 20 min.	gastric pH, acid volume, concentration, output at hourly intervals from 24:00 - 08:00.
08:00	last samplings of gastric content and blood, NG and IV removed	

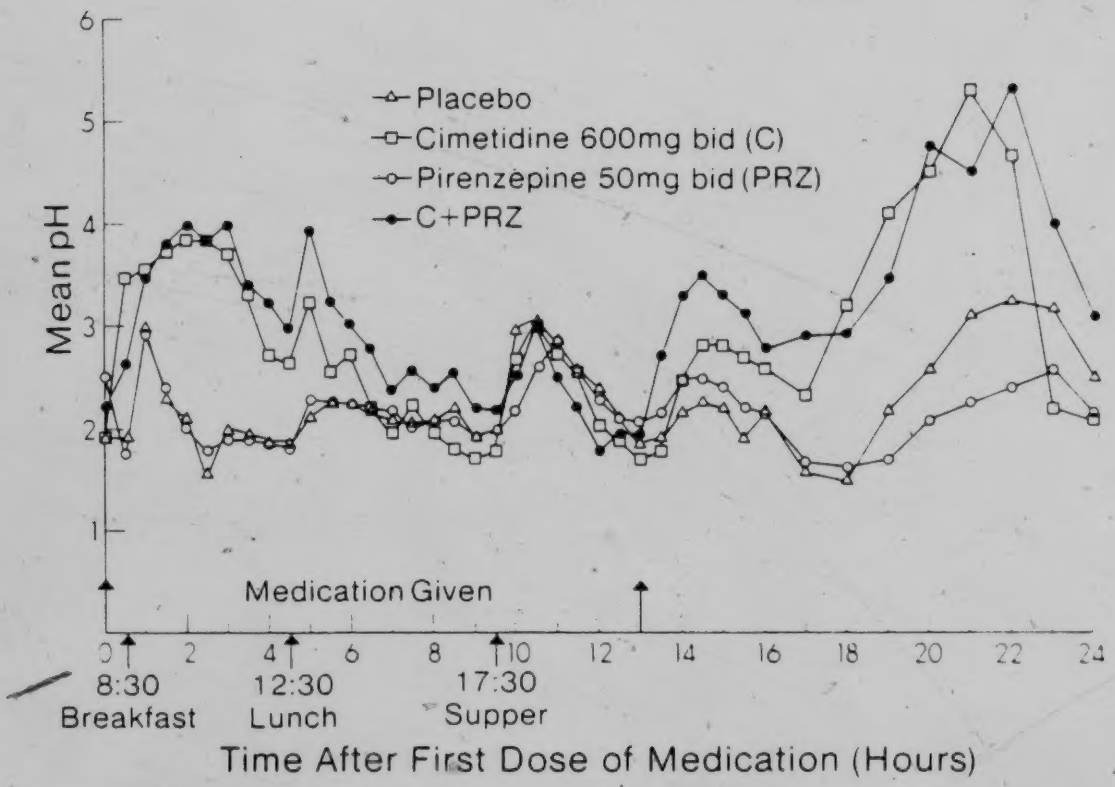

Figure 1. Mean intragastric pH values over the 24-hour period.

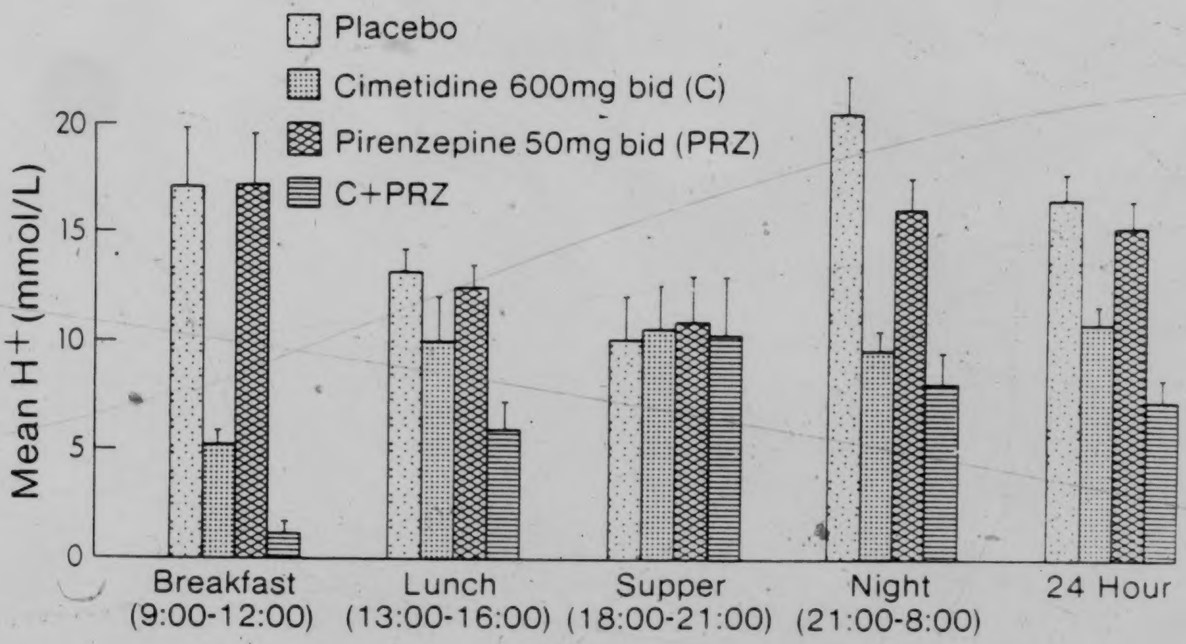

Figure 2. Mean intragastric H^+ activities after each meal, overnight, and over the 24-hour period, Mean ± SEM.

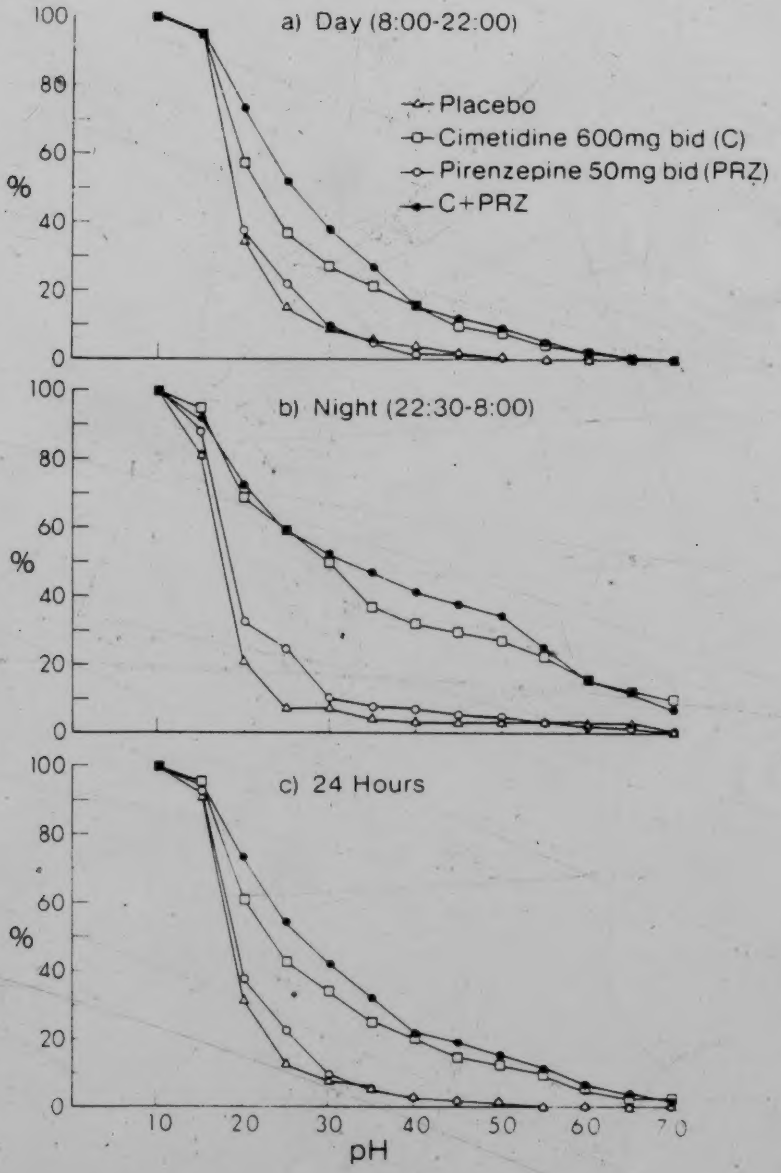

Figure 3. Cumulative percentages of pH readings at or above each pH from 1.0 to 7.0 a) daytime, b) nighttime, c) 24-hour.

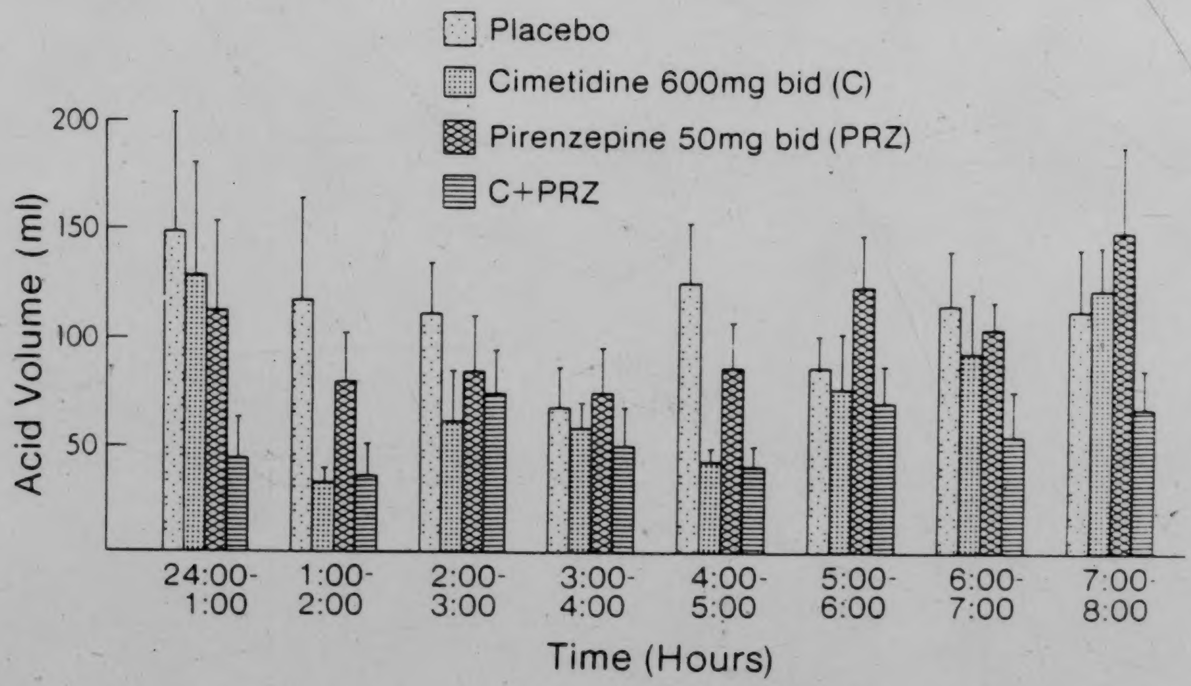

Figure 4. Mean nocturnal acid secretory volume at hourly intervals from 24:00 to 08:00 hr, mean ± SEM (ml).

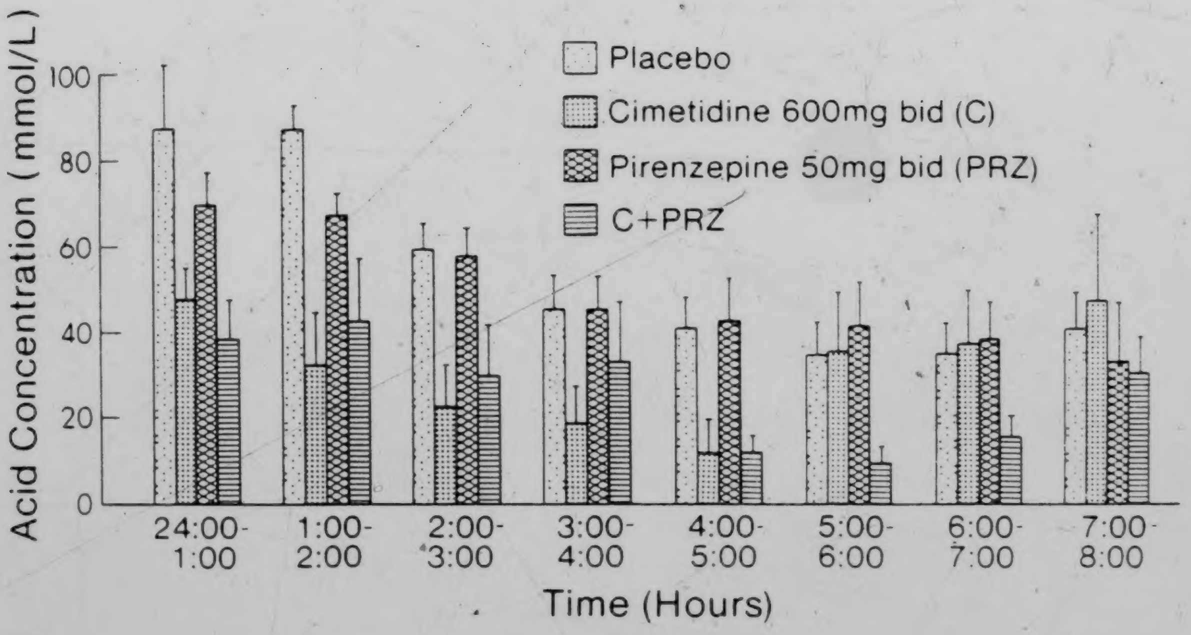

Figure 5. Mean nocturnal acid concentration at hourly intervals from 24:00 - 08:00 hr, Mean ± SEM (mmol/L).

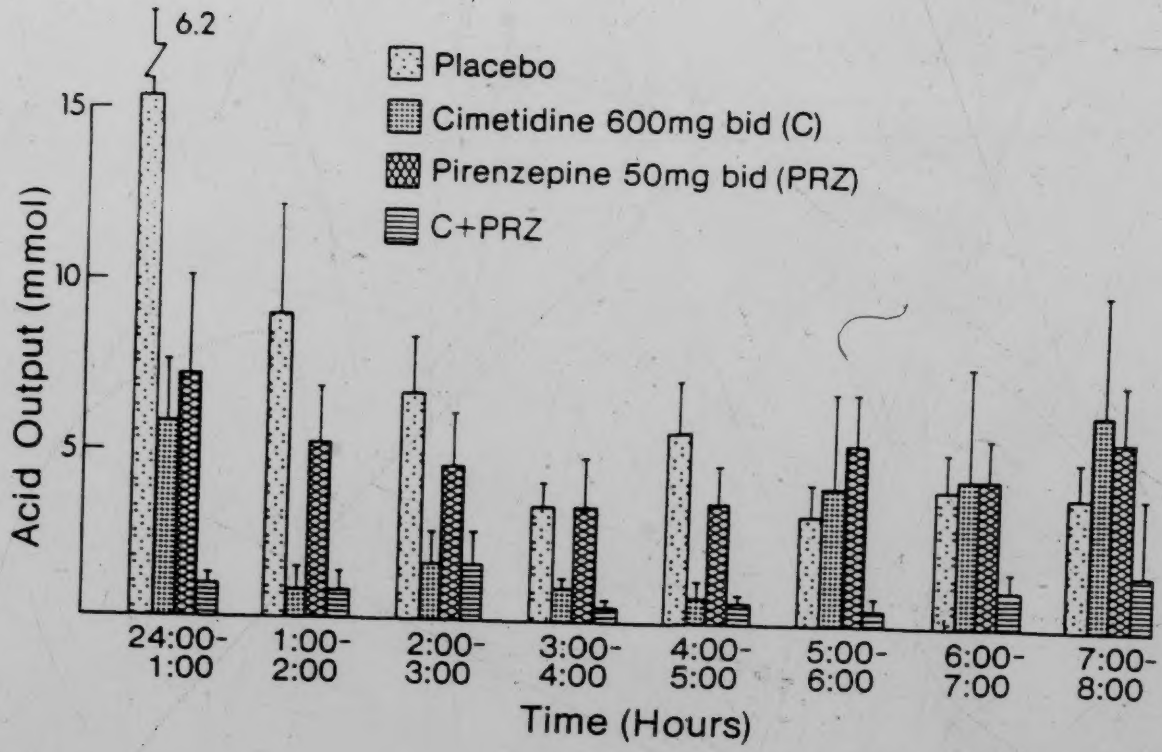

Figure 6. Mean nocturnal acid secretory output at hourly intervals from 24:00 to 08:00 hr, Mean ± SEM (mmol).

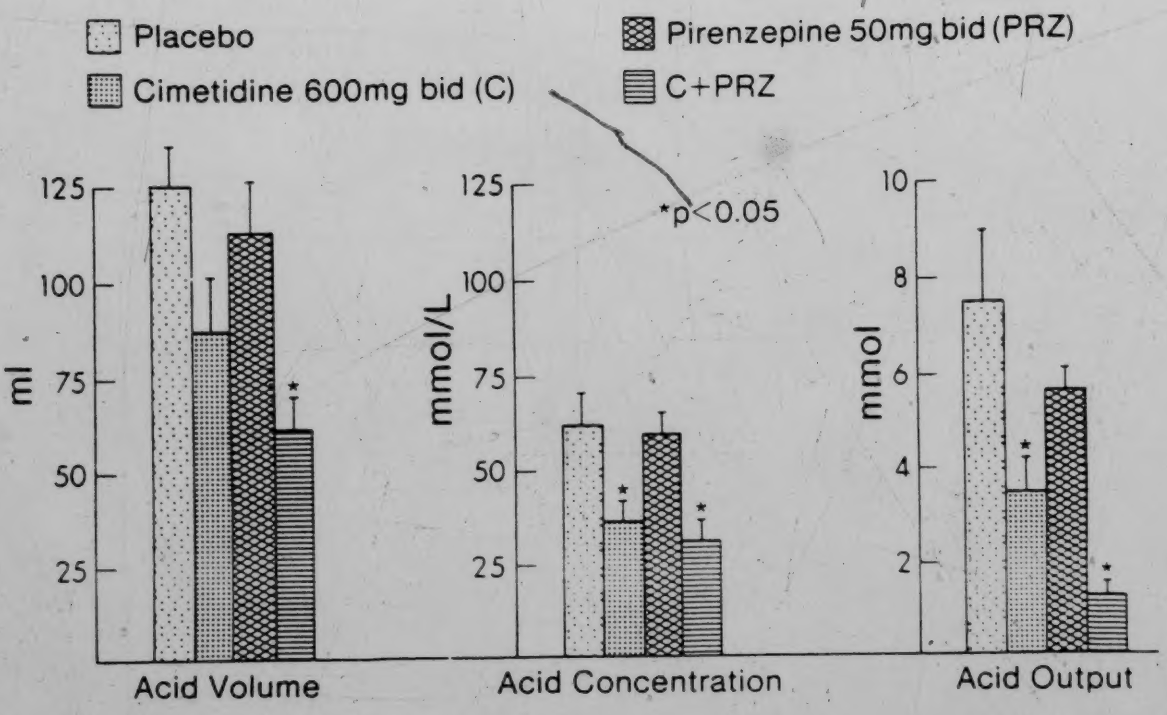

Figure 7. Mean hourly acid volume, acid concentration, and acid output overnight (24:00 - 08:00 hr), Mean ± SEM.

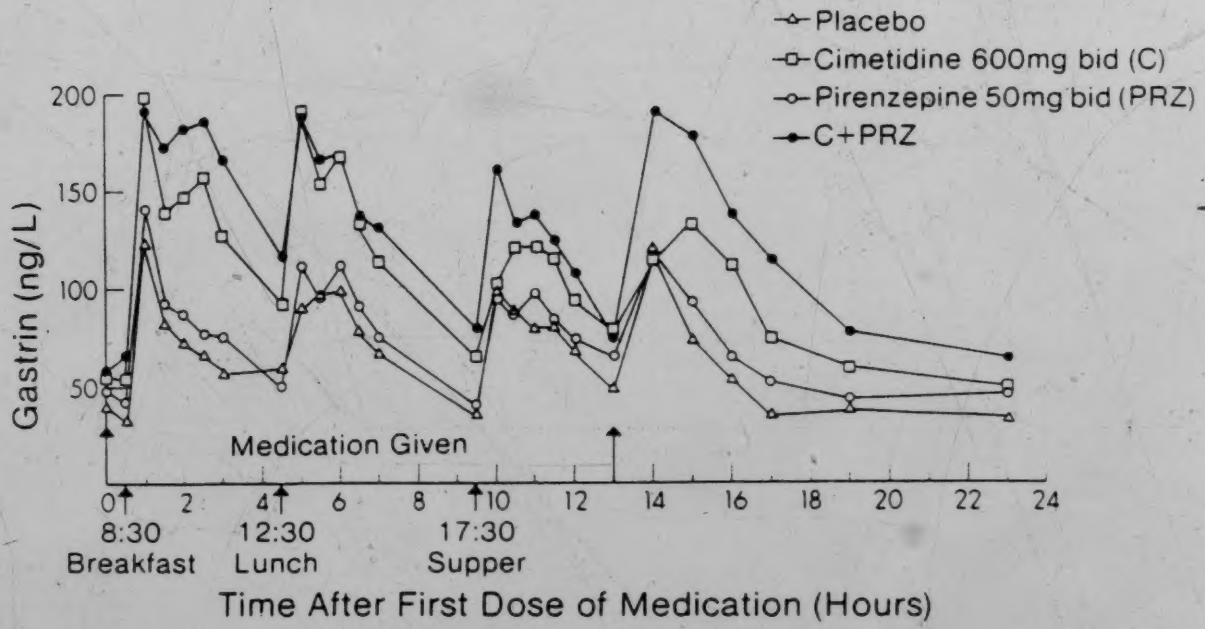

Figure 8. Mean serum gastrin concentration over 24-hour period, Mean ± SEM (ng/L).

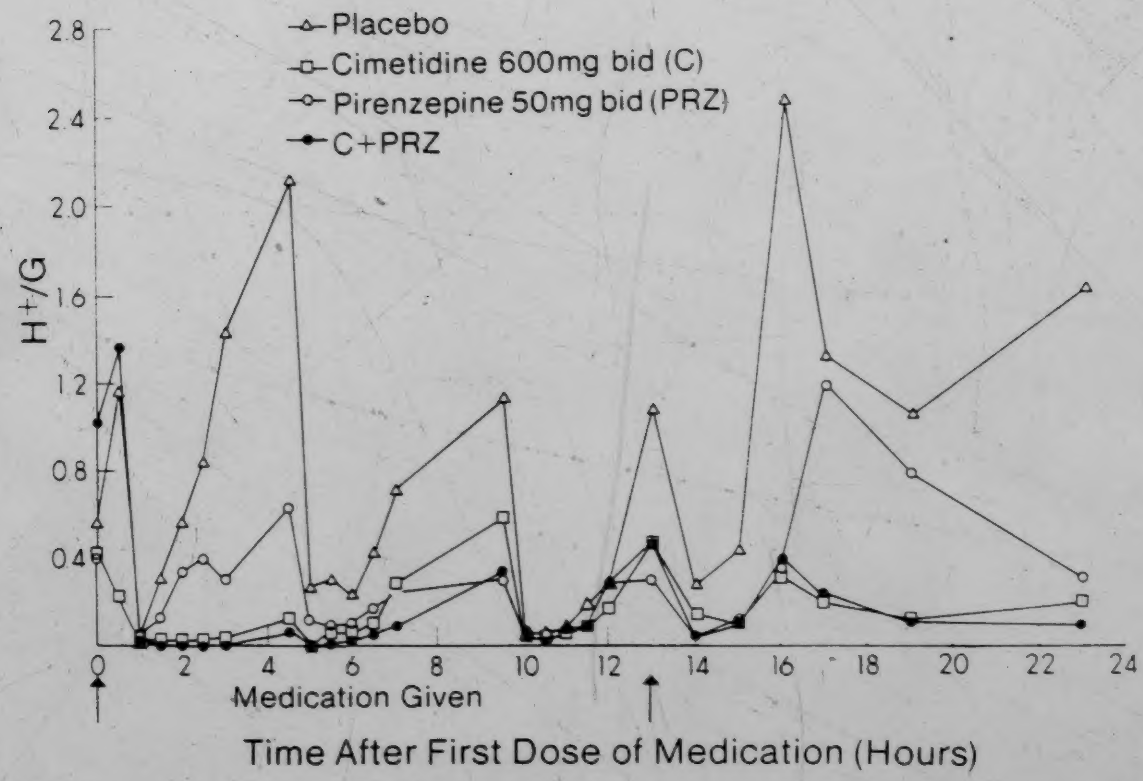

Figure 9. Mean ratio of H^+ activities and serum gastrin concentration (H^+:G) over 24-hour period.

7. ENPROSTIL, A DEHYDRO-PROSTAGLANDIN E_2, HAS POTENT ANTISECRETORY AND ANTIGASTRIN PROPERTIES IN PATIENTS WITH DUODENAL ULCER DISEASE

SUMMARY

This study was designed to compare the effects of Enprostil (E), a synthetic dehydro-prostaglandin E_2, on 24-hour intragastric pH and serum gastrin profile in patients with duodenal ulcer (DU) disease. The dosing regimen included E 35 mcg hs, E 70 mcg hs and E 35 mcg bid, compared with cimetidine 600 mg bid (C), and placebo (P). Ten patients with inactive DU were randomly assigned to all five treatment regimens for one week each according to a Latin Square Design. There was a one week washout period between each treatment. Intragastric pH and serum gastrin measurements were carried out on the last day of each treatment week. In P, intragastric pH rose after each meal and fluctuated between 1.5-3.5. E 35 mcg bid and C elevated pH after breakfast and during the night ($p<0.05$). The single nighttime dose of E had a marked effect on pH only when given in the dose of 70 mcg and this effect lasted over 13.5 hours. The pH values during the night were similar in the groups treated with E 35 mcg bid and E 70 mcg hs. During the daytime, the readings at or above pH 4 were P 5%, C 21%, E 35 mcg bid 34%. During the nighttime, the readings >4 were P 12%, C 29%, E 35 mcg bid 39%, E 35 mcg hs 19% and E 70 mcg hs 38%. The postprandial rise in serum gastrin was greatly enhanced by C, but the change after breakfast was dramatically blunted by E 35 mcg bid. The gastrin concentration was increased in C during the night but there was no difference in gastrin concentration overnight between all regimens of E and P. This study suggests that 1) E 35 mcg bid is as effective as C 600 mg bid in suppressing postprandial and nocturnal intragastric acidity; 2) E 35 mcg bid and 70 mcg at night are similarly potent in suppressing nocturnal acidity; 3) in addition to its cytoprotective effect, Enprostil has potent antisecretory and antigastrin properties.

INTRODUCTION

Prostaglandin methyl analogues given orally inhibit gastric acid secretion in response to food and various secretagogues in animals and humans[1,2] in a dose-dependent manner. The mechanism of acid inhibition is unknown. Recent studies suggested that the serum gastrin response to a meal may be inhibited by low doses of methyl PG E_2 given orally or intravenously[2,3]. However, serum gastrin was shown to be increased by an antisecretory dose of prostacyclin[4].

Several clinical trials have suggested the beneficial effect of prostaglandin methyl analogues on the healing of duodenal ulcer[5,6]. This ulcer healing property of these prostaglandins may be related in part to their acid inhibiting effect[7]. Intragastric pH monitoring has been a useful technique to assess the effect of potential antisecretory agents[8,9], and to modify the dosage regimen in patients with duodenal ulcer or with acid hypersecretion to achieve an optimum therapeutic effect[10]. Our previous study showed that cimetidine 600 mg bid is superior to cimetidine 300 mg qid in suppressing intragastric acidity in patients with inactive duodenal ulcer[11]. Both regimens of cimetidine exaggerated the gastrin responses after meals but had no effect on the basal gastrin concentration. The present study was designed to compare the effects of three dosage regimens of Enprostil (Syntex, RS-84135-00-00-3), a synthetic dehydro-prostaglandin E_2, and cimetidine on 24-hour intragastric pH and serum gastrin profile in patients with inactive duodenal ulcer disease.

MATERIALS AND METHODS

1. Patient Population

The study population consisted of five male and five female subjects with a past history of duodenal ulcer, previously documented on endoscopy. The patients were currently asymptomatic and were not receiving other antisecretory agents at the time of the study. All patients were free of active systemic disease and had no past history of vagotomy or gastric surgery. Their average age was 42.4 ± 4.4 years (range 25 - 64 years). None of the patients were smokers. Before entry into the study, all patients had a pentagastrin test (6.0 mcg/kg, subcutaneously). The mean (±SE) basal acid output (BAO) was 7.4 ± 4.7 mEq/hr. In response to pentagastrin, the mean maximal acid output (MAO) was 37.4 ± 7.1 mEq/hr, with the values over 35 mEq/hr in three subjects.

The study was approved by the Ethics Committee of the Department of Medicine, University of Alberta, and informed consent was obtained for each patient prior to the study.

2. Study Design

A Latin Square design was used in which each patient received all possible treatment regimens consisting of Enprostil 35 mcg h.s., 70 mcg h.s., 35 mcg bid, cimetidine 600 mg bid, and placebo, in a randomized sequential order. Each treatment regimen was administered for one week each and each patient was hospitalized for intragastric pH and serum gastrin analyses over 24-hour period on the last day of each treatment week. There was a one week washout period between each treatment week, during which time the patients were on no medication.

3. Trial Procedure

Each patient was admitted to a special allocated clinical investigation unit on the night prior to the study day. This ensured that the nighttime dose of medication was administered before the conduct of the pH monitoring. All subjects followed the protocol as outlined in Table 1. They were fasted overnight after 24:00 hr and water was permitted ad libitum. At 07:00, a nasogastric tube was positioned under fluoroscopic control, so that the tip was in the most dependent part of the stomach. Intravenous infusion of a 0.9% saline solution was initiated at a rate sufficient to keep the vein open to allow free access for sampling of venous blood. The first dose of drug or placebo was given at 08:00 hr, and the nighttime dose was administered at 20:00 hr. All vital signs and subjective symptoms were monitored during the study period. The patients were ambulant and were encouraged to entertain themselves on the ward.

The patients were non-smokers and thus did not smoke during the study period. The subjects were provided with a choice of meals similar to our previous study[11]. The patients consumed an average of 1556 ± 44 kcal/day (range 1305 - 1780 kcal/day), comprising an average of 173 gm of carbohydrate, 70 gm of protein, and 65 gm of fat. The approximate calories provided by carbohydrate, protein and fat were 48%, 17%, and 35%, respectively. For each patient, there was no difference in food intake during each of the five study periods. The average daily fluid intake was 2.5 L.

4. Intragastric pH Monitoring

The method used for intragastric pH monitoring has been published[11]. Gastric acidity was monitored over the 24-hour period: 5 ml samples of gastric juice were aspirated every 30 minutes while the patient was awake, and at 60 minute intervals after midnight. A 5 ml flush of 0.9% saline solution was used, if necessary, to obtain sufficient gastric juice for pH measurement, and to wash the syringe used to aspirate the gastric content. The pH of each sample was measured to the nearest 0.10 unit using a combined glass and reference electrode and pH meter which had been calibrated with standard buffers (pH 2.0, 4.0 and 7.0) before each batch of measurements. The aspirate was then returned to the stomach to assure complete availability of medication.

The effects of all treatment regimens on intragastric pH values during the day, overnight and over the 24-hour period were evaluated. As peptic activity is markedly diminished at pH 4.0[12], cumulative percentages of readings at or above this pH were compared between each treatment group. Each pH measurement was converted to hydrogen ion (H^+) activity using the standard table for analysis[13].

5. Serum Gastrin Profile

Serial blood samples were drawn through the intravenous line, then were centrifuged, and the serum was immediately separated and stored at -4° C for determination of serum gastrin concentration. Serum gastrin concentration (ng/L) was measured by radioimmunoassay method using a commercial kit (Schwarz-Mann) which measures both G-34 and G-17. The integrated gastrin reaponse (IGR) after each meal was calculated by obtaining the area under the curve (AUC) from each meal time, to the time that serum gastrin concentration approached its basal value. The basal concentration present at mealtime was taken into account by calculating the AUC over the same time period from this basal value and subtracting the basal values from the overall AUC after each meal. The relationship of H^+ and serum gastrin concentrtion was studied in all treatment groups.

6. Statistical Analysis

P-values for treatment effects were calculated from the rank, transformed data. Sex, subject and order of treatment administration were taken into account for data analyses. The P-value less than 0.05 was considered to be statistically significant.

RESULTS

1. Intragastric pH Profile

The mean pH values for all treatment regimens are shown for the daytime hours (Figure 1) and for the nighttime hours (Figure 2). During the daytime hours (08:00 - 20:00), the pH values rose transiently after each meal in the placebo-treated patients, with the mean pH values ranged between 1.5-3.2. In the cimetidine and Enprostil treatment groups, the pH values ranged between 1.8-4.5. The mean pH values during the daytime were similar in the Enprostil 35 mcg hs and in the placebo group. The mean pH values for the Enprostil 70 mcg hs were significiantly above the mean values for the placebo group between 08:00 - 09:30; none of the other daytime values were different from the placebo group. In contrast, in the Enprostil 35 mcg bid group, there were marked differences in the mean pH values as compared with the placebo group (Figure 1). These differences were most pronounced after breakfast, plus some values were significantly above the mean values of the placebo group after lunch time. Similarly, the mean pH values in the cimetidine 600 mg bid group were higher than the mean values in the placebo group after breakfast, and at various intervals after lunch.

During the nighttime hours (20:00-08:00), the pH values in the placebo-treated group fluctuated between 1.8-3.3 (Figure 2). When Enprostil was given as 35 mcg hs, the mean values for the pH during the nighttime hours were significantly higher than placebo values only between 3.5-6.0 hours after dosing. Following the evening dose of 35 mcg Enprostil to the patients receiving the twice daily dosage regimen, the gastric pH values were significantly above placebo values between 3.5-12.0 hours after dosing. With Enprostil 70 mcg hs, mean intragastric pH values were significantly greater than placebo between 3.5-12.0 hours after dosing. Indeed, when the intragastric pH values were monitored into the daytime hour following the nighttime administration of 70 mcg Enprostil, the mean intragastric pH values were significantly above placebo values for 13.5 hours after dosing (Figures 1 and 2). Following the nighttime dose of cimetidine 600 mg bid, the intragastric pH values were significantly higher than those in the placebo group at 2.5, 3.5-6, 10, and 12 hours after dosing (Figure 2).

During the daytime, the mean intragastric pH values in the patients treated with Enprostil 35 mcg bid were numerically higher than the pH values in patients treated with cimetidine 600 mg bid, but none of these differences achieved statistical significance. Similarly, during the nighttime hours, there was no significant inter-group mean pH values. Thus, there was no difference in the mean pH values of the nighttime pH regimen in the Enprostil 35 mcg bid versus the Enprostil 70 mcg hs groups.

Cumulative percentages of the pH readings at or above a given pH from 1.0 to 7.0 are shown in Figure 3. During the daytime (Figure 3a), less than 5% of the pH readings were > 4.0 in the placebo-treated patients. There was no difference between placebo, Enprostil 35 mcg hs and Enprostil 70 mcg hs groups in the percentage of pH reading > 4.0 during the daytime period. In contrast, 21% of the daytime pH readings were > 4.0 in the cimetidine group, and 34% of the pH readings were > 4.0 in the 35 mcg bid group. Although a numerically greater proportion of pH readings were > 4.0 in the Enprostil 35 mcg hs during the nighttime as compared with the placebo group, these differences failed to achieve statistical significance (Figure 3b). While 29% of the pH readings were > 4.0 in the cimetidine group during the night, greater than 38% of the pH readings were > 4.0 in the Enprostil 35 mcg bid and in the Enprostil 70 mcg hs groups (Figure 3b). When the results of the daytime and nighttime hours were combined and assessed for the 24-hour period, only 7% of the pH readings were equal to or greater than 4.0 in the placebo group (Figure 3c). A similar percentage of pH readings > 4.0 was observed in the Enprostil 35 mcg hs group as compared to the placebo group. Although 18% of the pH readings were > 4.0 in the 70 mcg hs Enprostil group, the most dramatic difference was noted in the Enprostil 35 mcg bid group, with more than 35% of the pH readings > 4.0. This mean value was numerically greater than that in the cimetidine group (21%). Thus, when considering daytime, nighttime, and 24-hour results, the greatest proportion of pH readings were equal to or greater than 4.0 in the Enprostil 35 mcg bid group.

The pH values were converted to intragastric H^+ activities and the results following each meal and overnight are summarized in Figure 4. The mean intragastric H^+ activities were significantly suppressed by cimetidine and Enprostil 35 mcg bid after breakfast, overnight and during the 24-hour period. The overnight H^+ activities were suppressed by Enprostil 70 mcg hs to a similar extent as the suppression observed with Enprostil 35 mcg bid. Although the mean values of the nighttime (20:00 - 08:00) intragastric H^+ were lower in the Enprostil 35 mcg hs group as compared to the placebo group , the difference was not statistically significant.

2. Serum Gastrin Concentrations

The mean basal serum gastrin concentration was 48.40 ± 6.06 ng/L in the placebo-treated group. After each meal the serum gastrin concentration in the placebo-treated group increased to a similar magnitude with the average maximal concentration of 136.67 ± 31.63 ng/L. The peak concentration was attained within 60 minutes after each meal (Figure 5).

In patients treated with cimetidine 600 mg bid, the serum gastrin concentration rose after each meal. Most of the mean values for the serum gastrin concentration during the daytime hours were significantly higher in the cimetidine treated group as compared to those values observed for the serum gastrin concentration observed in the patients treated with placebo. In the cimetidine-treated group the serum gastrin concentration achieved a significantly higher peak concentration after each meal. With Enprostil 35 mcg bid, the serum gastrin concentration failed to increase after breakfast, with persistently lower gastrin concentrations over two and a half hour period after breakfast as compared to placebo. Indeed, the effect of Enprostil 35 mcg bid on the serum gastrin concentration after breakfast was striking at one hour, since ten out of ten (100%) of the study patients had lower gastrin levels after Enprostil 35 mcg bid than after placebo. Seven of these ten subjects (70%) had gastrin levels reduced to at least 50% while on Enprostil 35 mcg bid as compared with placebo. In contrast, when a single dose of Enprostil was given at bedtime either as the 35 mcg or the 70 mcg group, the serum gastrin concentration increased after each meal, including after breakfast, in a similar fashion as in the placebo group.

In the placebo-treated patients, there was an increase in the gastrin concentration after each meal, and the integrated gastrin response was similar after breakfast, after lunch, and after supper (Table 2). The post-prandial integrated gastrin responses after each meal were higher in the cimetidine as compared with the placebo-treated patients, although the difference was significant only after breakfast (Table 2). While the integrated gastrin response was similar in the Enprostil 35 mcg bid versus the placebo group after lunch and after supper, the integrated gastrin response after breakfast was significantly lower in the Enprostil 35 mcg bid as compared with the placebo group. The integrated gastrin response was thus markedly lower after breakfast in patients given Enprostil than in patients given cimetidine. The post-prandial integrated gastrin responses after all meals were similar in the Enprostil 35 mcg hs, Enprostil 70 mcg hs, and in the placebo group.

During the nighttime hours, the serum gastrin concentrations were similar in all Enprostil groups and in the placebo group. In contrast, the gastrin concentration was significantly higher in the cimetidine group than in the placebo group over the 1.5 - 4.0 hour period after the evening dose of cimetidine (Figure 5). Due to the prolonged gastrin response observed with cimetidine after suppertime, the integrated gastrin responses were also calculated from 17:30 - 24:00 hr. Only the value in the cimetidine-treated group was significantly higher than in the placebo-treated group (Table 2).

3. Ratio of Hydrogen Ion Activity to Serum Gastrin Concentration

In the placebo-treated patients, the ratio of the hydrogen ion activity to the serum gastrin concentration (H^+/G) rose after each meal (Figure 6). The ratio of H^+/G was dramatically reduced in the cimetidine-treated patients. During the datyime, the ratio of H^+/G was similar in the Enprostil 35 mcg hs, Enprostil 70 mcg hs and the placebo groups (Figure 6). Enprostil 35 mcg bid exerted both a daytime and a nighttime effect on intragastric pH and serum gastrin concentration (Figures 1, 2 and 5). The ratio of H^+/G was intermediate in the Enprostil 35 mcg bid group between the values in the placebo-treated patients and the suppressed values in the cimetidine-treated patients, despite the greater acid inhibition in this Enprostil group. The nightime H^+/G values in all Enprostil-treated groups were intermediate between the high value in the placebo group and the low value in the cimetidine group.

DISCUSSION

Enprostil, a dehydro-prostaglandin E_2, is a potent antisecretory agent. When given in an oral dose of 35 mcg twice daily, Enprostil was at least as effective as cimetidine 600 mg twice a day in suppressing H^+ activities after breakfast, overnight and over the 24-hour period (Figures 1-4). Although the mean pH values were similar in these two treatment regimens, pH readings remained > 4.0 for longer periods in the Enprostil 35 mcg bid than in the cimetidine group, both during the daytime and during the nighttime (Figure 3).

A single dose of Enprostil 35 mcg given at 20:00 hr only had effects on intragastric pH from 3.5-6.0 hr after dosing. The effect of Enprostil 35 mcg bid on the daytime pH was striking up to 6 hours after the morning dose, although in some patients there was an additional effect on pH values until 8.5 hr after the dosing. After the evening dose of Enprostil 35 mcg bid, the effect on intragastric pH persisted throughout the nighttime. The duration of action was even more prolonged with a higher dose: when the nighttime dose was doubled to 70 mcg, the effect on intragastric pH lasted 13.5 hours, but the nocturnal pH values were not significantly different than those of Enprostil 35 mcg given twice daily. The daytime pH values were also higher in the Enprostil 70 mcg hs group, but only for the first hour after breakfast. These results suggest that Enprostil suppresses intragastric H^+ activities in a dose-dependent manner, but that the duration of action is influenced both by the dose of medication and by the frequency of dosing. The explanation for this carry-over effect when the medication is given in divided doses has not been established in this study. Clearly, Enprostil 35 mcg bid is superior to the other regimens, as it exerts a prolonged effect on pH both during the daytime and during the nighttime.

The serum gastrin response to a meal is under the influence of vagal stimulation[14], gastric distension[15], and the presence of food in the stomach[16]. Food-stimulated acid secretion is partly under the control of gastrin[16]. The pH remained between 1.5-3.3 in the placebo-treated group, with only transient elevation of pH for a short duration after each meal, possibly due to the buffering effect of food. The gastrin response to a meal is thought to be at least partially under the negative feedback control of gastric acidity[17]. Thus, it was not surprising that the higher gastrin response after each meal was observed in the cimetidine-treated patients whose intragastric H^+ activities were suppressed after meals. However, it is likely that cimetidine and Enprostil influence gastrin levels by some mechanism(s) in addition to their effect on intragastric acidity, since these medications altered the H^+/gastrin ratio (Figure 6).

Interestingly, the gastrin response to a meal was suppressed markedly for a 2.0 hour period after breakfast by Enprostil 35 mcg bid, despite the presence of marked gastric acid suppression. Furthermore, the gastrin responses were lower in all Enprostil groups as compared to cimetidine groups after the nighttime dose of medication. This suggests that Enprostil has antigastrin properties, in addition to potent antisecretory properties. Previous results have been conflicting as to the effects of different forms of prostaglandins on serum gastrin concentration[2,3,4]. The effect on gastrin may be related to the type of prostaglandin or to the route of its administration. Prostaglandin is believed to decrease gastric acid secretion from parietal cells by inhibiting cyclic-AMP formation[18,19], but the mechanism of the effect of prostaglandin inhibition of gastrin release in response to food is unknown. It is uncertain from this study what proportion of the prostaglandin-related inhibition of acid secretion is due to the blunting of the food-stimulated gastrin response, or to a direct effect on acid production and release.

The development of a peptic ulcer is believed to occur when there is an imbalance between the aggressive factors of acid and pepsin, and defensive factors related to mucosal resistance and mucosal protection. Several prostaglandins have a "cytoprotective" property unrelated to gastric acid inhibition[20]. The mechanism of this mucosal defense has not been established, although it may relate to the properties of prostaglandin in enhancing mucus and bicarbonate production, strengthening the mucosal epithelial junction, and increasing mucosal blood flow. The antisecretory and antigastrin properties of Enprostil suggest that this prostaglandin may prove to be beneficial in the healing of peptic ulcers.

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Table 1

TRIAL PROCEDURE

Times	Procedure	Sampling
19:00	admitted to metabolic ward medication given at 20:00 hr NPO after midnight, water *ad libitum*	
07:00	NG tube placed under fluoroscopy, 0.9% saline infusion	
08:00	medication	gastric pH measurement every 30 min from 08:00 to 24:00 hr. blood drawn every 30-60 min after each meal
08:30	breakfast	
10:30	morning snack	
12:30	lunch	
14:30	afternoon snack	
17:30	supper	
20:00	medication	
20:30	bedtime snack	
22:30	optimal bedtime snack encouraged to retire	
08:00	last gastric sample taken NG tube and IV infusion removed	gastric pH measurement every 60 min from 24:00 to 08:00 hr. blood drawn at 4 hr intervals

Table 2

POSTPRANDIAL INTEGRATED GASTRIN RESPONSES (ng.min/L), MEAN ± SEM

	Placebo	E 35 mcg hs	E 70 mcg hs	E 35 mcg bid	C 600 mg bid
Breakfast					
08:30-10:30	6432.0 ± 1538.1	6375.5 ± 1710.4	6541.5 ± 1799.3	1500.0 ± 337.3*	12325.5 ± 2392.4*
Lunch					
12:30-14:30	7609.5 ± 1701.8	9357.0 ± 2085.9	9504.0 ± 2383.9	7744.5 ± 2074.6	9679.5 ± 2396.4
Supper					
17:30-19:30	4797.0 ± 1307.8	6951.0 ± 1824.6	7309.5 ± 1994.3	8221.5 ± 2007.6	7164.0 ± 1883.3
17:30-24:00	8908.5 ± 2647.8	10369.5 ± 4417.3	10978.5 ± 3523.4	10261.5 ± 2950.7	15325.5 ± 4875.7*

$p < 0.05$ as compared to placebo

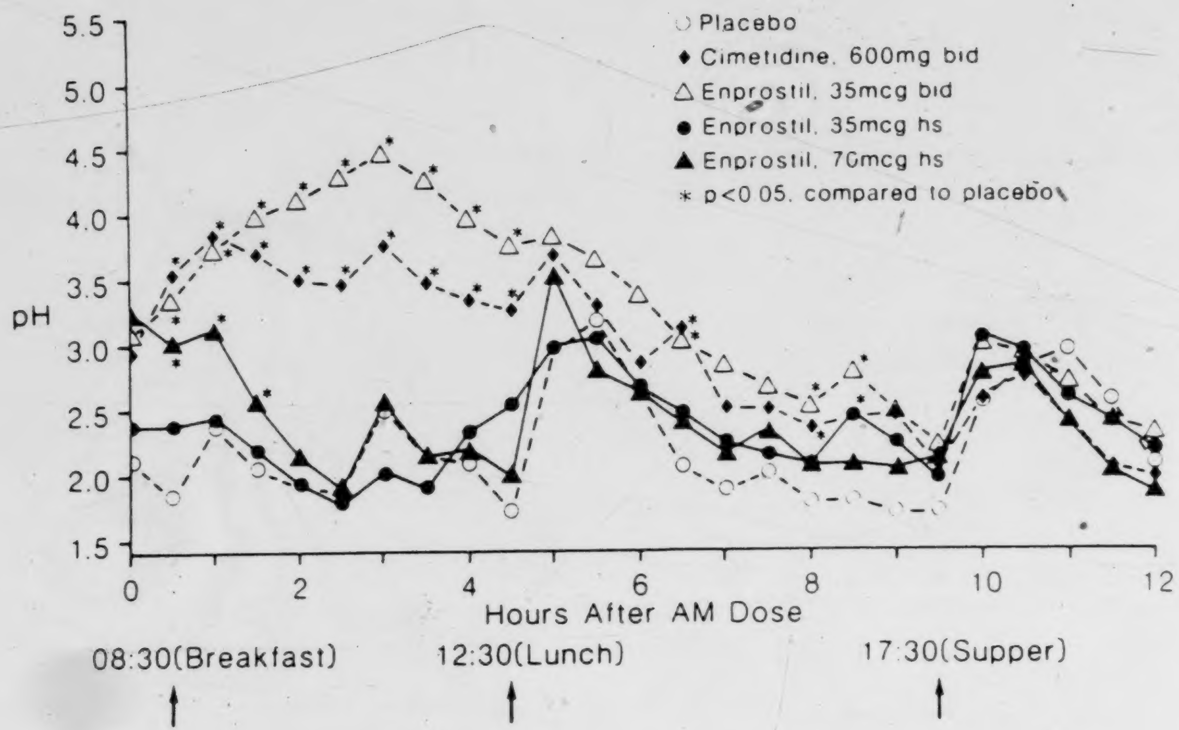

Figure 1. Mean intragastric pH values during the daytime (08:00-20:00).

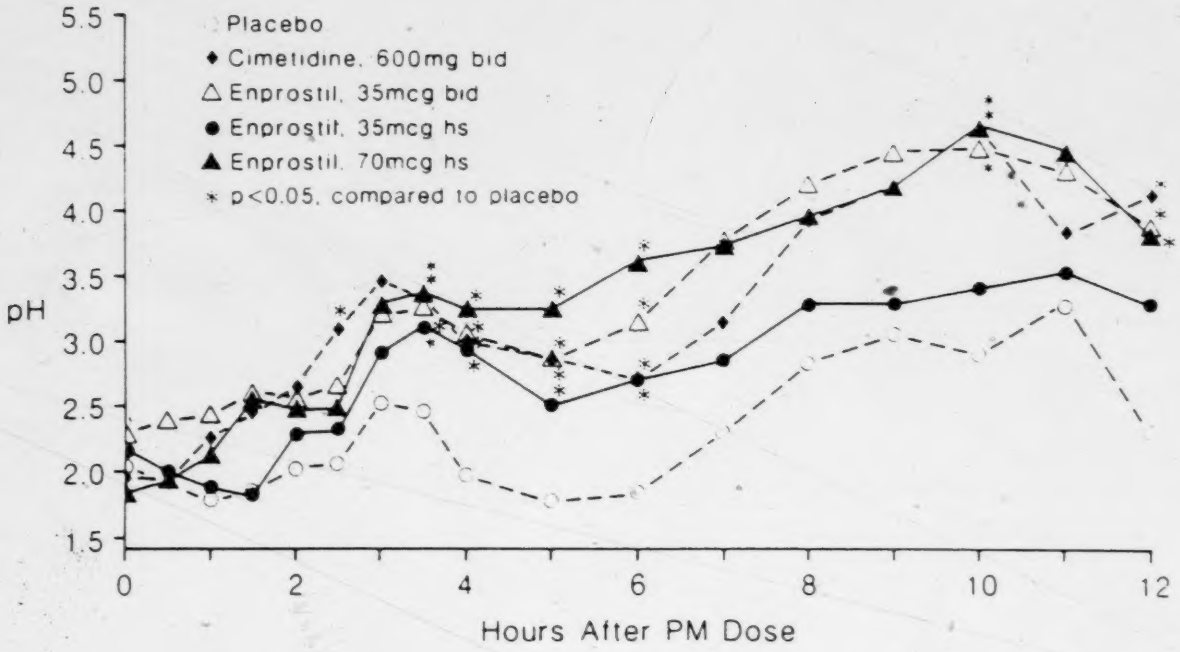

Figure 2. Mean intragastric pH values during the nighttime (20:00-08:00).

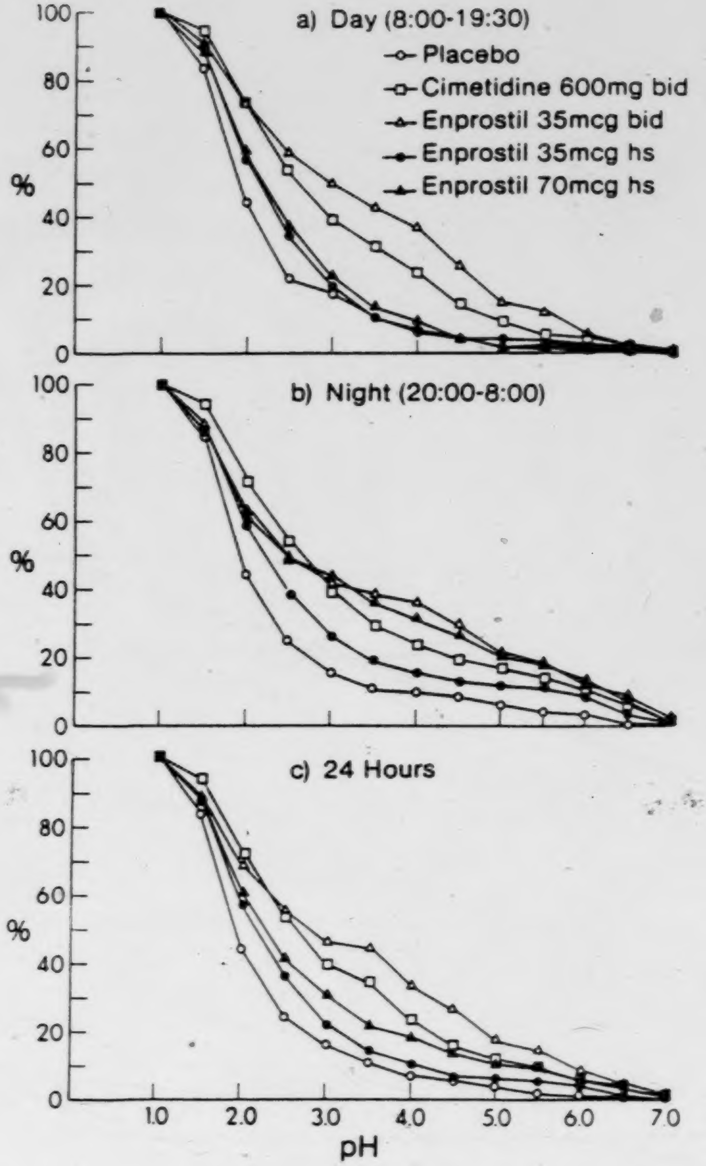

Figure 3. **Cumulative percentages of pH readings at or above pH values from 1.0-7.0 a) daytime, b) nighttime, c) 24-hour**

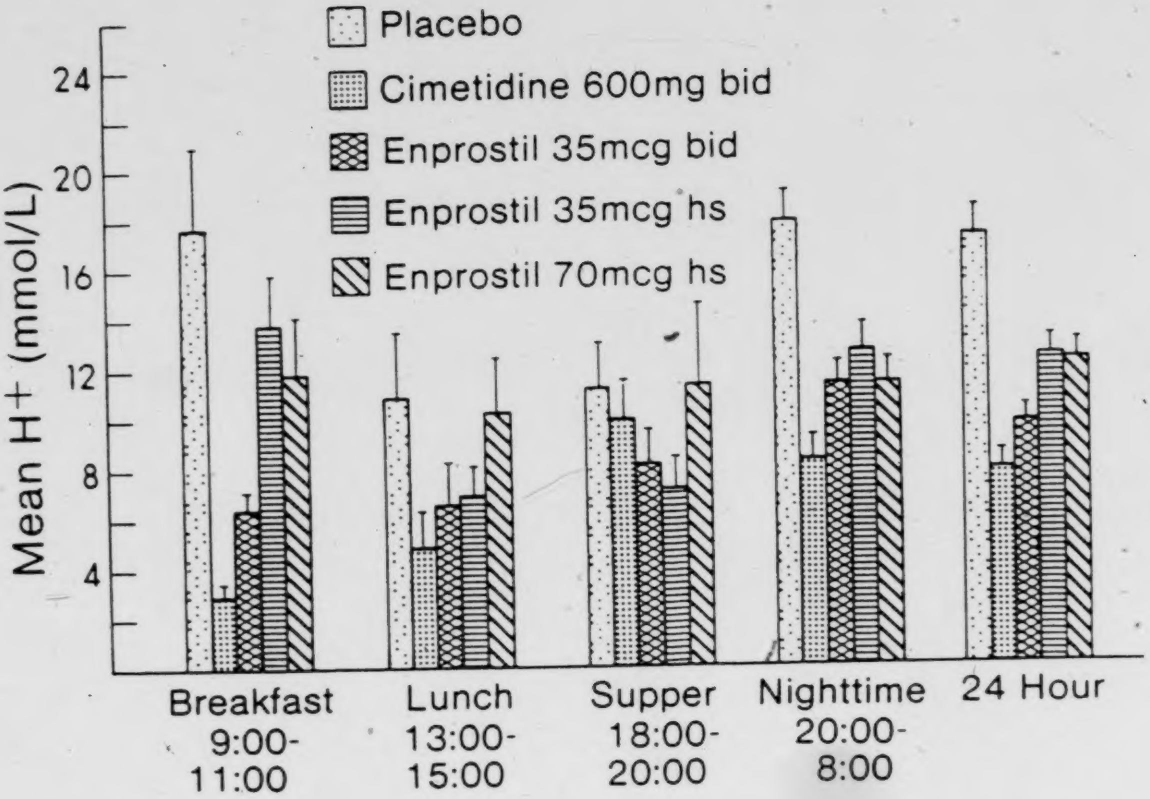

Figure 4. Mean intragastric hydrogen ion activities after meals, overnight and over 24 hour period (mmol/L).

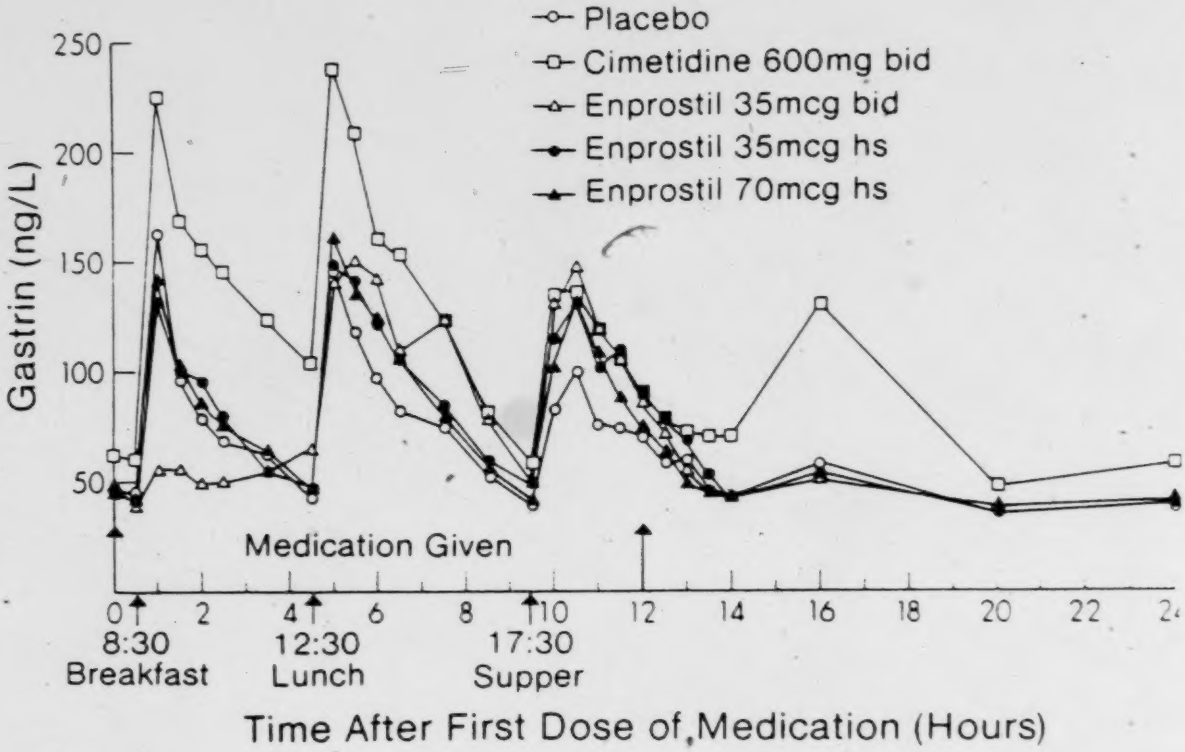

Figure 5. Mean serum gastrin concentration over 24 hour period (ng/L).

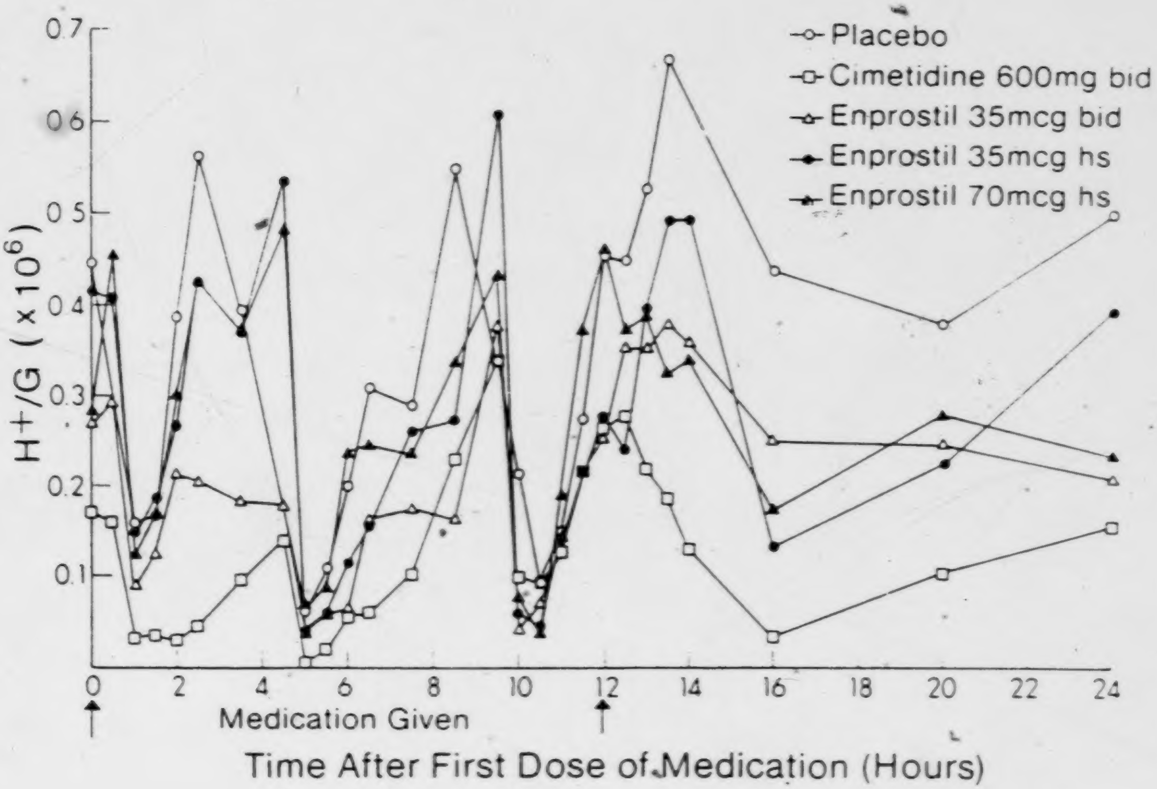

Figure 6. Ratio of H^+ and serum gastrin concentration (H^+/G) over 24 hour period.

8. INTERRELATIONSHIP BETWEEN GASTRIC ACIDITY AND GASTRIN CONCENTRATION IN PATIENTS WITH DUODENAL OR GASTRIC ULCER, AND NORMAL SUBJECTS

SUMMARY

Increased gastric acidity (H^+) may be important in the pathogenesis of duodenal ulcer (DU). The role of H^+ in gastric ulcer (GU) is less well defined. This study was undertaken to determine: 1) the 24-hour intragastric pH and gastrin (G) profiles in 31 DU, 8 GU and 7 healthy volunteer subjects (N), and 2) the effect of cimetidine 600 mg bid (C) on these measurements. The basal acid output (BAO) was higher in DU and lower in GU than in N but there were considerable overlaps; thus there was no statistical difference between the means. In response to pentagastrin, the peak acid output (PAO) was significantly higher in DU than that of GU or N. There was no difference between intragastric H^+ activities after meals, overnight and over the 24-hour period in DU, GU and N. However, the pH values remained at or above 4.0 for a longer period during the night in GU than in DU or N. There was no difference in the basal G concentration in all subject groups but the postprandial G response after each meal was higher in GU than in DU and in DU than in N. In GU, C was associated with H^+ suppression after all meals and overnight, whereas in DU and N, C suppressed H^+ only after breakfast and overnight. The G response to food was enhanced by C to a greater magnitude in DU and GU than in N. In N, the ratio of H^+:G was higher than in DU or GU but was suppressed only minimally by C whereas marked suppression of H^+:G was observed in DU and GU with C. Cimetidine is effective in H^+ suppression in all subject groups and may alter the sensitivity of parietal cell to gastrin.

In summary, patients with a past history of duodenal or gastric ulcers differed from normal volunteers in their food-stimulated gastrin response, and in their gastrin-response in patients taking cimetidine.

Cimetidine also accentuated the difference in H^+:G between DU or GU and N. In view of these differences in gastrin response to food, but not in their intragastric pH in response to food, it is suggested that defective control of or response to gastrin may be more important than the intragastric activity in the pathogenesis of acid-peptic disease.

INTRODUCTION

There are many abnormalities which may be important in the pathogenesis of duodenal and gastric ulcer disease (1,2). The role of gastric acid in the pathogenesis of duodenal ulcer (DU) is generally accepted. These patients tend to have higher stimulated acid secretion in response to food and secretagogue than normal subjects (3,4). The defective feedback control of gastric acid on gastrin release may be responsible for the higher gastrin response to food in duodenal ulcer patients (5). The role of gastric acid in gastric ulcer (GU) is less well defined. The acid secretory capacity has been shown to vary depending on the location of the ulcer and its association with duodenal ulcer (6,7). However, one of the approaches to the therapy of gastric ulcer has been aimed at the reduction of gastric acid. Gastrin concentration has been reported to be higher in some gastric ulcer patients than in normal subject (8). This higher gastrin concentration may be related to lower intragastric acidity or to increased G-cell sensitivity or stimulation as a result of delayed gastric emptying in gastric ulcer as compared to normal subjects (9).

Cimetidine has been shown to be beneficial in the healing of both duodenal ulcer and gastric ulcer (10,11). Our previous study showed that cimetidine 600 mg given twice daily suppressed the 24-hour intragastric acidity and enhanced gastrin response to food in patients with inactive duoudenal ulcer disease (12). However, the 24-hour intragastric concentrations and the effect of cimetidine on these measurements have not been reported in patients with gastric ulcer disease. Accordingly, the present study was designed to: 1) compare 24-hour intragastric pH and serum gastrin profiles in patients with duodenal or gastric ulcer disease, and in normal subjects and 2) determine the effect of cimetidine 600 mg bid on these measurements in the three subject groups.

MATERIALS AND METHODS

The study population consisted of 31 subjects with inactive duodenal ulcer disease, 8 subjects with inactive gastric ulcer disease and 7 normal subjects. Only 23 out of 31 duodenal ulcer subjects were randomized to cimetidine 600 mg bid and placebo treatment. A double-blind, cross-over study was used in which each subject received cimetidine 600 mg bid and placebo for one week each. Each subject was hospitalized on the last day of the treatment week over 24-hours for intragastric pH and serum gastrin and drug level measurements. The other 8 subjects with duodenal ulcer were studied after the placebo treatment as part of other studies. All patients with either duodenal ulcer or benign gastric ulcer previously documented on upper endoscopy were found to have healed. They were not receivng medication at the time of the study. None of them had previous vagotomy or gastric resection for their ulcer disease. They were free of other significant systemic diseases. All normal sujbects were free of gastrointestinal complaints including peptic ulcer symptoms and none of them had a past history of gastrointestinal disease. Endoscopy was not performed on these healthy volunteers.

Descriptive characteristics of each subject group are shown in Table 1. There were 19 males and 12 females in the duodenal ulcer group. Their mean age was 41.6 ± 2.4 years (range 23 - 67 years). The mean duration of disease was 4.9 years. There were 7 females and 1 male in the gastric ulcer group. Their mean age was 48.3 ± 14.7 years (range

19 - 64 years). The mean duration of diseae was 7.1 years. The ulcers were previously located in the gastric antrum in 6 out of the 8 patients. Only 2 patients had ulcer in the body of the stomach. Only 1 patient was taking excessive aspirin during the time gastric ulcer was previously diagnosed. None of the patients were taking ulcerogenic medication at the time of study. Eleven subjects with duodenal ulcer were smokers whereas 5 gastric ulcer patients and 1 normal subject smoked. There was no change in the patients' smoking habit during the study period. None of the subjects abused alcohol. Physical examination, hematological and biochemical tests of each subject remained normal during the study period.

Before entry into the study, all subjects had a pentagastrin stimulation test (6.0 mcg/kg subcutaneously).

The project was approved by the Ethics Committee of the Department of Medicine, University of Alberta, and informed consent was obtained from each patient prior to the study.

TRIAL PROCEDURE

On the last day of each treatment week, patients were admitted at 7:30 a.m., after an overnight fast. A strict protocol was then followed (12). A nasogastric tube, size Fr. 14-16, was passed and positioned in the most dependent part of the stomach under fluoroscopic control. Intravenous line was established with 0.9% saline solution at a rate to keep vein open sufficient to allow free sampling of venous blood for serial determinations of serum gastrin and serum cimetidine concentrations. The standardized meal similar to our previous study (12) was provided so that identical caloric intakes and proportions of macronutrients were consumed by each subject during the study periods. Patients were encouraged to refrain from alcohol and smoking but if the patient continued to smoke, the number of cigarettes consumed were recorded on the study day. Vital signs were monitored during the study period and all subjective symptoms were recorded.

INTRAGASTRIC pH MEASUREMENT

Gastric samples in the amount of 5 ml were aspirated every 30 minutes during the day and every 60 minutes during the sleep hours. The pH of each gastric sample was measured to the nearest 0.10 unit using a combined glass and reference electrode and pH meter. The pH electrode was calibrated with standard buffer of pH 2.0, 4.0 and 7.0 before each batch of measurements. The samples were then returned to the stomach content to ensure complete absorption of the drug.

The pH values were plotted over a 24-hour period in subjects treated with cimetidine and placebo. The cumulative percentages of pH readings at or above pH 1.0 - 7.0 were calculated in all treatment groups. The cumulative percentages of pH readings $\geq$ 4.0 was chosen as a point of comparison between the treatment groups as peptic activity is markedly decline at pH 4.0 (13).

The result of each pH measurement was converted to hydrogen ion activity (H^+) using standard table (14) for analysis. The effect of cimetidine on H^+ in all subject groups was determined over a specific period after each meal, overnight and over 24-hour period.

SERUM GASTRIN CONCENTRATION

Blood samples were drawn every 30 minutes over a two hour period after each meal and at two to four hour intervals during the night. Samples were centrifuged and separated immediately, then stored at -4°C for further determinations of serum gastrin concentration. A commercial radioimmunoassay kit was used to measure serum gastrin concentration. The antibody employed measured both G-17 and G-34.

The total postprandial gastrin responses over a four hour period were calculated by obtaining the total area under the curve from mealtime to four hours after each meal using the trapezoidal rule.

STATISTICAL METHOD

The mean intragastric pH and gastrin concentrations were calculated in each subject group when receiving cimetidine or placebo. Mean intragastric H^+ activities converted from pH values at specific time periods were compared using analysis of variance to determine the difference between groups. The effect of cimetidine in all subject groups were compared by adjusting to the placebo values. The F-test was applied at the 5% level of significance to determine the overall difference. The pairwise difference was tested using Student-Newman-Keuls test when there was overall difference.

RESULTS

1) Basal and Stimualted Acid Output

There were marked variations of basal acid output (BAO) in 31 patients with DU, ranging from 0.1 to 43.0 mmol/hr (Figure 1). Ten out of 31 subjects with DU had BAO higher than 5.0 mmol/hr. The mean BAO in patients with DU was 6.0 ± 1.5 mmol/hr (Table 2). The mean BAO in 8 patients with GU was 0.8 ± 0.4 mmol/hr with the range of 0.1 - 2.5

mmol/hr. None of the GU patients had a BAO greater than 3 mmol/hr. The mean BAO in normal subjects was 3.0 ± 1.7 mmol/hr, and only 1 volunteer had a BAO greater than 5 mmol/hr. Due to overlaps of BAO in DU, GU and normal subjects, the differences in BAO in three subject groups failed to achieve statistical significance.

In response to pentagastrin (6.0 mcg/kg, subcutaneously), the mean maximum acid output (MAO) in DU group was 41.0 ± 3.1 mmol/hr (Table 2). The MAO was higher than 35.0 mmol/hr in 16 out of 31 (52%) of the subjects with DU. The mean MAO was higher in DU subjects than in normal subjects, with considerable overlap between patients with DU and normal subjects. The difference failed to reach a statistically significant level. The MAO in patients with GU overlapped with the values in normal subjects (Figure 2). However, the mean MAO was significantly lower in GU subjects than in DU subjects. The mean peak acid output was significantly higher in patients with DU than in patients with GU or normal subjects (Table 2).

2) Twenty-four Hour Intragastric pH Profiles and H^+ Activities

In the 7 normal subjects, the pH values ranged between 1.7 - 3.0 during the 24-hour period when treated with placebo (Figure 3). In subjects with DU, the pH values fluctuated between 1.7 - 2.9 over the 24-hour periods, with the mean pH of 2.2 ± 0.7 during placebo treatment (Figure 4). The pH values varied between 1.2 - 3.9 in the GU subjects treated with placebo (Figure 5).

During the 24-hour period, only 2.5% of the pH readings remained at or above 4.0 in the normal subjects treated with placebo (Table 3). Following placebo treatment, the percentage of pH readings ≥ 4.0 was numerically higher in patients with GU than patients with DU, whose values in turn were higher than in normal subjects. However, the differences between all groups were not statistically significant. During the daytime period the percentage of pH readings $\geq$ 4.0 was similar in all groups. During the night, the percentage of pH readings $\geq$ 4.0 was significantly higher in subjects with GU than in DU subjects or normal subjects. The percentages of pH readings $\geq$ 4.0 during the night were similar in DU subjects and normal subjects.

The mean H^+ activities over the 24-hour period was 16.14 ± 1.75 mmol/L in subjects with DU treated with placebo (Figure 6). This value was not statistically different from the 24-hour mean H^+ activities in either placebo-treated gastric ulcer subjects or placebo-treated normal subjects. Similarly, the H^+ activities after each meal were not different between each subject group treated with placebo. The H^+ activities were numerically highest after breakfast and during the night in all groups.

3) Serum Gastrin Concentration

The mean basal gastrin concentration was 24.3 ± 3.4 ng/L in normal subjects treated with placebo (Table 4). The mean basal gastrin concentration was numerically higher in GU patients treated with placebo than in normal subjects (49.0 ± 9.4 ng/L vs 24.3 ± 3.4 ng/l. This difference was not statistically significant. The value of the mean basal gastrin concentration was intermediate between these values in the DU patients following placebo treatment (37.5 ± 3.3 ng/L).

After each meal the gastrin concentration rose approximately 170% in normal subjects and 210% in patients with DU or GU following placebo treatment. The average peak gastrin concentration in normal subjects was 66.7 ± 8.7 ng/l (Table 4). The peak gastrin concentration after each meal was numerically higher in both DU patients and GU patients than in normal subjects, with the mean peak gastrin concentration of 117.0 ± 2.3 ng/L and 150.8 ± 15.6 ng/L in DU subjects and GU subjects, respectively. The gastrin responses calculated over a 4 hour period after each meal are shown in Table 4. After each meal, the gastrin response was higher in DU patients and GU patients than in normal subjects. The difference between the DU group and normal subjects was significant only after breakfast ($p < 0.05$). The gastrin responses were significantly higher in the GU patients than in normal subjects after all meals. The gastrin responses after each meal was numerically higher in GU patients as compared to DU patients but only the difference after supper was significant ($p < 0.05$).

4) Effect of Cimetidine on Gastric Acidty and Gastrin Concentration

The effects of cimetidine 600 mg bid on gastric acidity and gastrin concentration were studied in 23 DU patients, 8 GU patients and 7 normal subjects. In all subject groups cimetidine was associated with higher pH values when compared to the placebo-treated values (Figures 3 - 5).

Adjusted to the placebo values the effect of cimetidine 600 mg bid on intragastric pH values were similar after breakfast, after lunch, overnight and over a 24-hour period in all subject groups (Table 5). After supper the effect of cimetidine on intragastric pH was greater in GU patients than those in DU patients and in normal subjects (Table 5). Cimetidine suppressed H^+ activities after breakfast, overnight, and over a 24-hour period in normal subjects (Figure 7) and in DU subjects (Figure 8). The H^+ activities were suppressed at all time periods in GU subjects (Figure 9).

The gastrin concentration increased slightly with cimetidine after breakfast and lunch in normal subjects but the difference of gastrin response after each meal was not significant in this normal subject group when treated with cimetidine or placebo (Figure 10). The gastrin response after each meal was greatly enhanced by cimetidine in DU and GU subjects (Figures 11, 12). The difference of postprandial gastrin response between the cimetidine-treated group and the placebo-treated group was significant after breakfast in DU and GU subjects.

c) Relationship of H^+ Activities and Gastrin Concentration

In all subject groups, the ratio of the H^+ activities and the serum gastrin concentration (H^+/G) fluctuated after each meal when the placebo was given (Figure 13, 14, 15). The values tended to be higher in normal subjects than in DU or GU patients. The ratio of H^+/G throughout the 24-hour period was markedly suppressed by cimetidine in both GU and DU subjects (Figure 14, 15). The ratio of H^+/G was suppressed by cimetidine only after breakfast in the normal subjects (Figure 13).

DISCUSSION

There is evidence to support the role of gastric acid in the pathogenesis of duodenal ulcer. Gastric acid secretion in response to sham feeding has been shown to be higher in duodenal ulcer patients than in normal controls (15). Increased acid secretory responses to secretagogues may be related to increased sensitivity of parietal cells to stimulation or greater number of parietal cell mass in duodenal ulcer patients (16,17). Increased duodenal acid load related to rapid gastric emptying is another possible mechanism in the pathogenesis of duodenal ulcer (18). Relationship between intragastric acidity and intraduodenal acidity has been previously shown (19).

The role of the gastric acid in gastric ulcer is less well defined than that of duodenal ulcer. The acid secretory capacity in gastric ulcer varies and thus may depend on the site of ulcer (6). However, the presence of low acidity does not totally exclude the role of acid in the formation of gastric ulcer. Increased H^+ back diffusion through the damaged mucosa may lead to loss of intraluminal H^+ (20). The concomitant gastritis may lead to impaired acid secretory capacity in gastric ulcer patients. Finally, the increased refluxed duodenal contents in gastric ulcer patients may provide sufficient neutralization of gastric contents (21,22). The role of gastric acid is suggested by the fact that ulcer rarely occurs in the presence of achlorhydria or in patients with pernicious anemia (23,24). Furthermore, acid inhibition by an H_2 blocker is associated with the healing of benign gastric ulcer (10).

In this study, we found marked variations of BAO in duodenal ulcer patients, with 10 out of 31 duodenal ulcer patients had BAO > 5.0

mmol/hr, whereas only 1 out of 7 normal subjects and none of the gastric ulcer patients had BAO > 5.0 mmol/hr. Acid secretion in response to pentagastrin tended to be higher in duodenal ulcer subjects than in normal subjects and was significantly higher than that of gastric ulcer subjects (Table 2). The MAO was > 35.0 mmol/hr in 16 out of 31 duodenal ulcer patients, whereas 2 out of 7 normal patients and 2 out of 8 gastric ulcer patients had MAO values exceeding 35.0 mmol/hr. This suggests that the basal acid secretory output is higher than normal control in a certain subgroup of duodenal ulcer subjects. In contrast, basal acid output in gastric ulcer patients is similar to normal subjects. This study was performed in patients with inactive duodenal or gastric ulcer. In DU, acid secretion decreases with the activity of the disease (25). The increased H^+ diffusion or impaired gastric secretory capacity from the inflammed tissue during the acute injury may lead to lower intraluminal H^+ in GU patients. However, this has not been described in duodenal ulcer patients.

Intragastric pH monitoring has been a useful technique to measure the effects of diet and drugs on intragastric pH over a prolonged period under physiological conditions closest to real life (26). Clinical responses to antisecretory agents in patients with Zollinger Ellison syndromes have been shown to correlate with their effect on 24-hour intragastric pH (27). By using this technique, it is not possible to measure the total acid secretory volume or acid output over this prolonged period with the presence of food in the stomach. This study suggests the similarity of intragastric pH profiles in subjects with duodenal ulcer, gastric ulcer and normal subjects. The H^+ activities after each meal, overnight and over the 24-hour period were not different between the three subject groups. However, the intragastric pH remained above 4.0 for a longer period during the night in gastric ulcer group than that of duodenal ulcer group or normal subject group. There was a similar diurnal variation of gastric acidity with the highest values after breakfast and during the night in all three subject groups.

It is not certain whether acid concentration or acid volume is more important in the formation of peptic ulcer. Indeed, the very idea of acid in the etiology of ulcer disease has been challenged (28). In spite of the generally accepted role of gastric acid, this study failed to confirm increased H^+ activities in duodenal ulcer or decreased H^+ activities in gastric ulcer as compared to normal subjects. Thus the differences between groups of patients is in basal or stimulated acid output and not in acid concentration. It may not be appropriate to assume the clinical significances of BAO, MAO in the pathogenesis of peptic ulcer disease. Gastric acid may only play a permissive role in peptic ulcer disease. It may allow the pepsin to be activated and cause damage to mucosa. The abnormality of pepsin secretion and its role in ulcer formation have not been fully elucidated. Pepsinogen I has been shown to be increased in some duodenal ulcer patients and their family members (29,30). The reduction of gastric acid by antisecretory agents in peptic ulcer disease will decrease peptic activity (13). This gastric acid suppression may only be an indirect measure in treating peptic ulcer disease.

Ulcer is believed to occur when there is an imbalance between the aggressive factors of acid, and pepsin, and the mucosal defense mechanisms. Several factors are important in maintaining the mucosa protection, including gastric mucus, unstirred water layer, bicarbonate secretion, gastric mucosal epithelium, mucosal blood flow, and mucosal metabolic function. Several medications are beneficial in the healing of both duodenal ulcer and gastric ulcer by their actions in improving mucosal defense (31,32). However, it is not known which of these factors in mucosal defense is impaired in peptic ulcer disease. Prostglandin may be important in protecting the gastric mucosa through several mechanisms. It is also interesting to speculate that the prostaglandin secretion in the duodenum in response to an acid load may be impaired in duodenal ulcer patients (33). In this study, the gastrin responses to food were higher in both duodenal ulcer and gastric ulcer as compared to normal subjects. In fact, there was a tendency of gastrin responses to be higher in gastric ulcer than in duodenal ulcer in this study. The lower H^+:G ratio in patients with duodenal and gastric ulcer subjects as compared to normal subjects suggested the decreased sensitivity of parietal cells to secrete acid in response to endogenous gastrin in these patients or the defective feedback control mechanism of gastric acid on gastrin release. This does not correspond with higher sensitivity of acid secretion to exogenous pentagastrin in duodenal ulcer patients.

When the effect of cimetidine 600 mg bid was studied in all subject groups, H^+ activity suppression was obtained after breakfast and overnight in duodenal ulcer and normal subjects, whereas suppression of H^+ activity was observed after all meals and during the night in gastric ulcer patients. The longer effect of acid suppression by cimetidine in gastric ulcer subjects cannot be explained by the difference of gastric acidity or serum gastrin concentration as compared to duodenal ulcer subjects or normal subjects. Food-stimulated gastrin response was enchanced by cimetidine to a greater extent in DU and GU than in normal subjects. The ratio of H^+:G was markedly suppressed by cimetidne in subjects with duodenal ulcer and gastric ulcer but minimally suppressed in normal subjects. Cimetidine thus accentuated the differences in the food-stimulated gastrin response and in H^+:G between patients with DU or GU and normal subjects. It is possible that an H_2 blocker may have an effect on the sensitivity of the G-cell to produce gastrin in peptic ulcer patients, in addition to its accepted effect on the parietal cell.

Gastric acidity may only play a permissive role in peptic ulcer disease. In order to prevent the occurrence or change the natural history of the disease, the primary etiologies need to be defined. Further studies are needed to determine the other etiologic mechanisms in peptic ulcer disease such as defective mucosal defence or altered pepsin secretion.

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Table 1. Characteristics of Subjects

	Normal subjects n = 7	Duodenal ulcer n = 31	Gastric Ulcer n = 8
Age (yrs) mean ± SEM	23.4 ± 1.8	41.6 ± 2.4	48.3 ± 14.7
Sex (male:female)	3:5	19:12	1:7
Smoking (no. of patients)	1	11	5

Table 2. Basal and Stimulated Acid Output, mean ± SEM

	Normal Subjects n = 7	Duodenal Ulcer n = 31	Gastric Ulcer n = 8
BAO (mmol/hr)	3.0 ± 1.7	6.0 ± 1.5	0.8 ± 0.4
MAO (mmol/hr)	28.0 ± 6.0	41.0 ± 3.1	20.7 ± 6.3†
PAO (mmol/hr)	22.9 ± 5.5	37.1 ± 2.6*	19.4 ± 6.3†

* $p < 0.05$, compared to normal subjects

† $p < 0.05$, compared to DU

Table 3. Cumulative Percentage of pH Readings (%) At or Above 4.0 During the Day, During the Night and Over the 24-hour Period Following Placebo Treatment, Mean ± SEM

	Normal Subjects n = 7	Duodenal Ulcer n = 31	Gastric Ulcer n = 8
24-Hour Period	2.5 ± 1.8	4.3 ± 1.0	9.4 ± 3.7
Day (0830 - 2200)	3.6 ± 2.6	3.5 ± 1.2	4.0 ± 2.7
Night (2230 - 0830)	0	5.6 ± 1.8	21.9 ± 9.0*†

* $p < 0.05$, compared to normal subjects

† $p < 0.05$, compared to DU

Table 4. Serum Gastrin Concentration and Postprandial Gastrin Responses Following Placebo Treatment, Mean ± SEM

	Normal Subjects n = 7	Duodenal Ulcer n = 31	Gastric ulcer n = 8
Basal gastrin concentration (ng/L)	24.3±3.4	37.5±3.3	49.0±9.4
Peak gastrin concentration (ng/L)	66.7±8.7	117.0±2.3	150.8±15.6
Postprandial gastrin responses			
Breakfast (0830-1230)	1963.9±563.7	3703.4±348.3*	4581.1±769.1*
Lunch (1230-1630)	2327.7±277.3	4160.1±419.7	5828.0±1044.3*
Supper (1730-2130)	2643.8±279.6	4132.9±372.1	6510.5±1322.2*†

* $p < 0.05$, compared to normal subjects

† $p < 0.05$, compared to DU

Table 5. Mean Intragastric pH Values After Meals, Overnight and Over 24-Hour Period When Cimetidine 600 mg bid was Administered

	Normal Subjects n = 7	Duodenal Ulcer n = 31	Gastric Ulcer n = 8
Breakfast (0900-1100)	3.47	3.74	4.18
Lunch (1300-1500)	2.90	2.95	3.79
Supper (1800-2000)	2.63	2.43	3.39*†
Overnight	3.31	3.67	3.31
24-Hour	2.87	3.18	2.87

All pH values were adjusted to the placebo pH values

* $p < 0.05$, compared to normal subjects

† $p < 0.05$, compared to DU

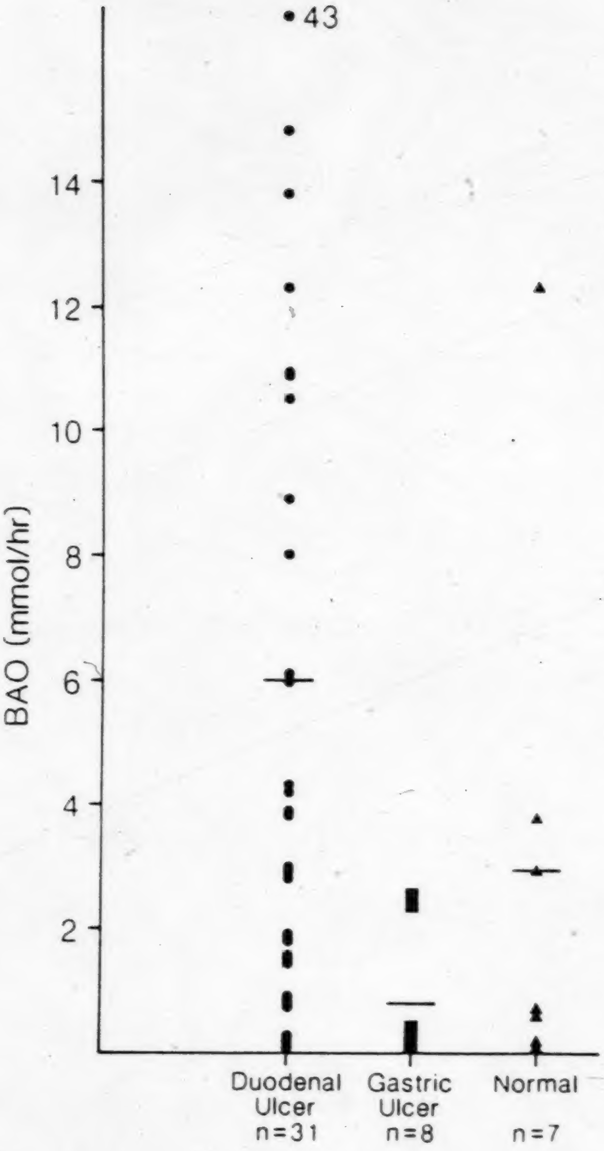

Figure 1. Basal acid output (mmol/hr) in patients with duodenal ulcer, gastric ulcer and normal subjects.

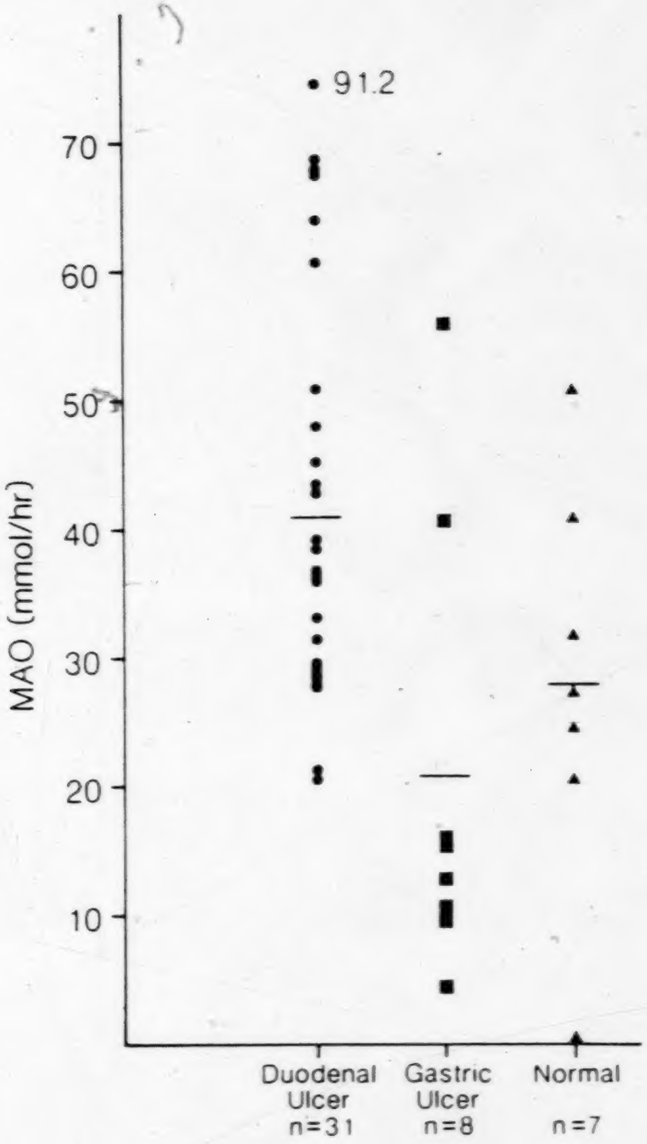

Figure 2. Maximal acid output (mmol/hr) in response to pentagastrin (6.0 mcg/kg, subcutaneously) in patients with duodenal ulcer, gastric ulcer and normal subjects.

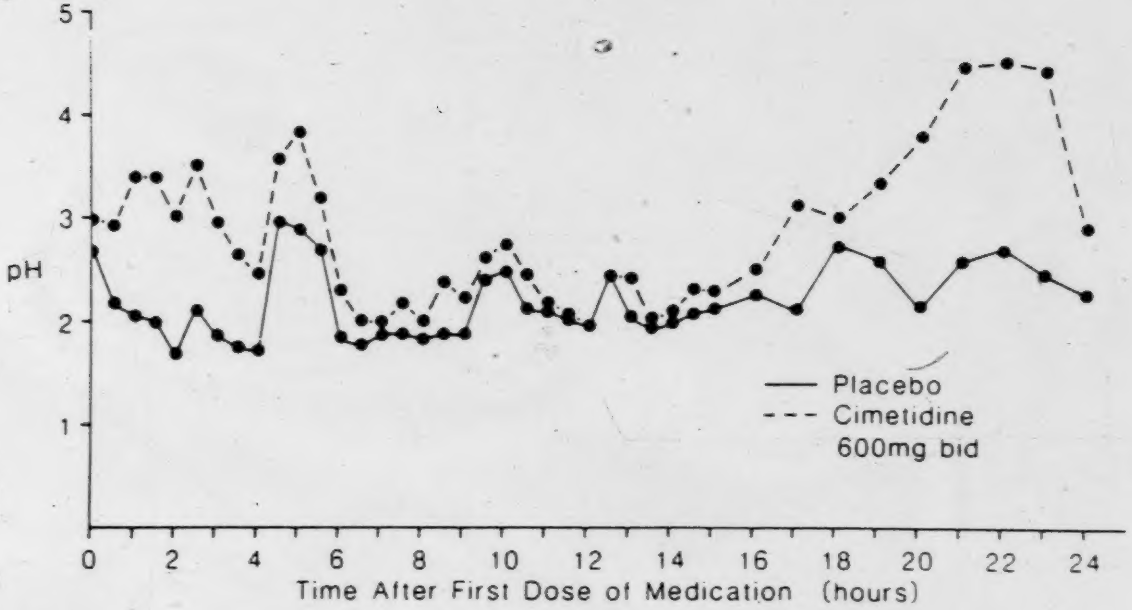

Figure 3. Mean intragastric pH over 24-hour period in normal subjects (n = 7) treated with cimetidine 600 mg bid and placebo.

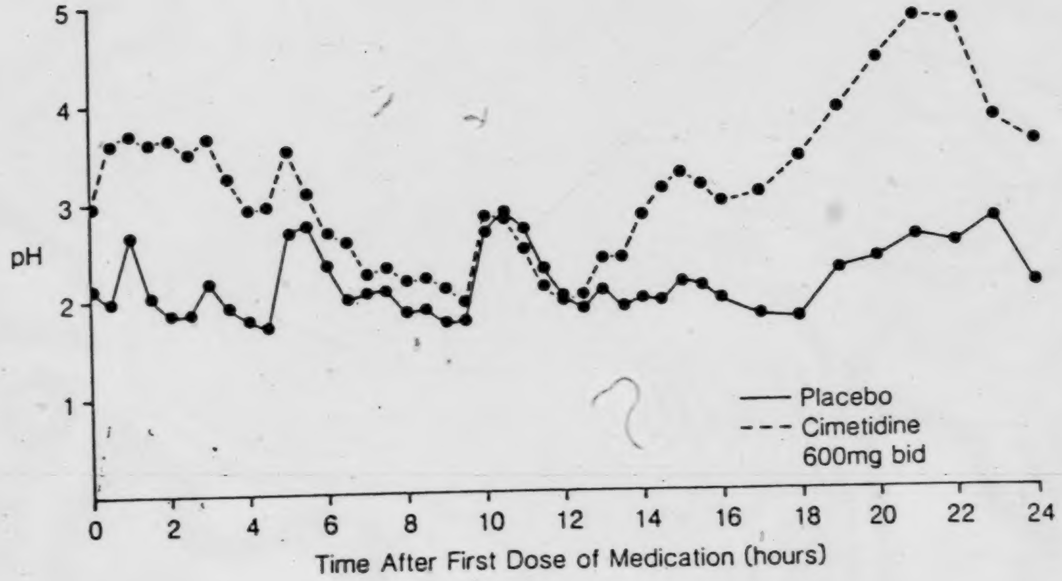

Figure 4. Mean intragastric pH over 24-hour period in duodenal ulcer patients (n = 23) treated with cimetidine 600 mg bid and placebo

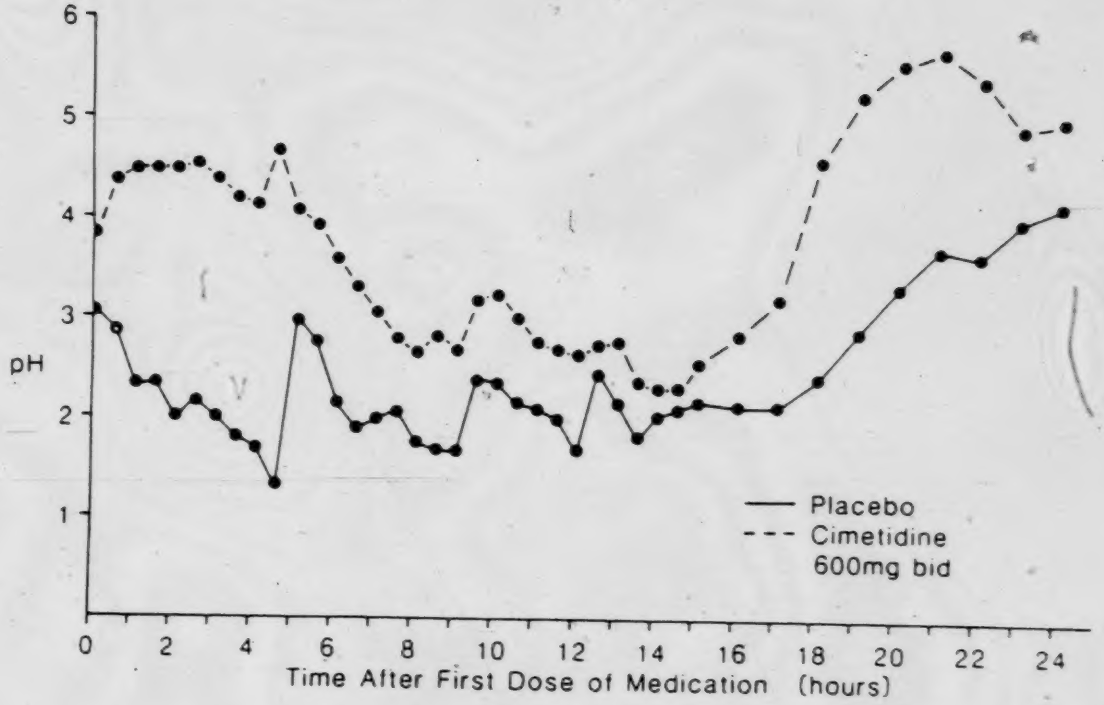

Figure 5. Mean intragastric pH over 24-hour period in patients with gastric ulcer (n = 8) treated with cimetidine 600 mg bid and placebo.

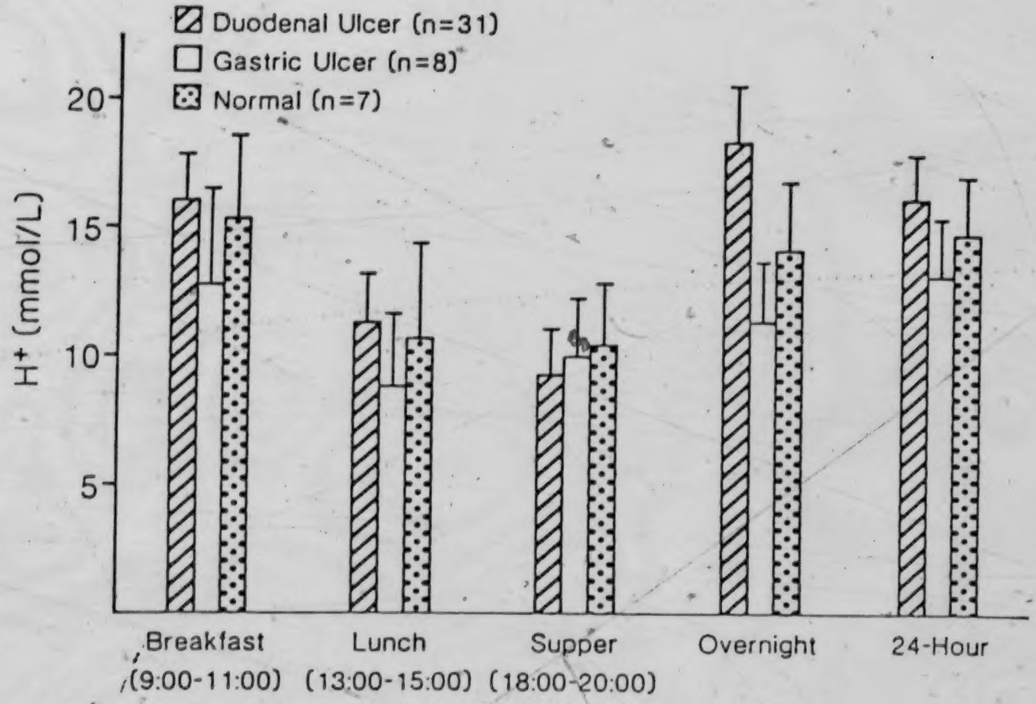

Figure 6. Mean intragastric H^+ activities after meals, overnight and over 24-hour period in patients with duodenal ulcer, gastric ulcer and normal subjects when placebo was administered (mmol/L), mean ± SEM

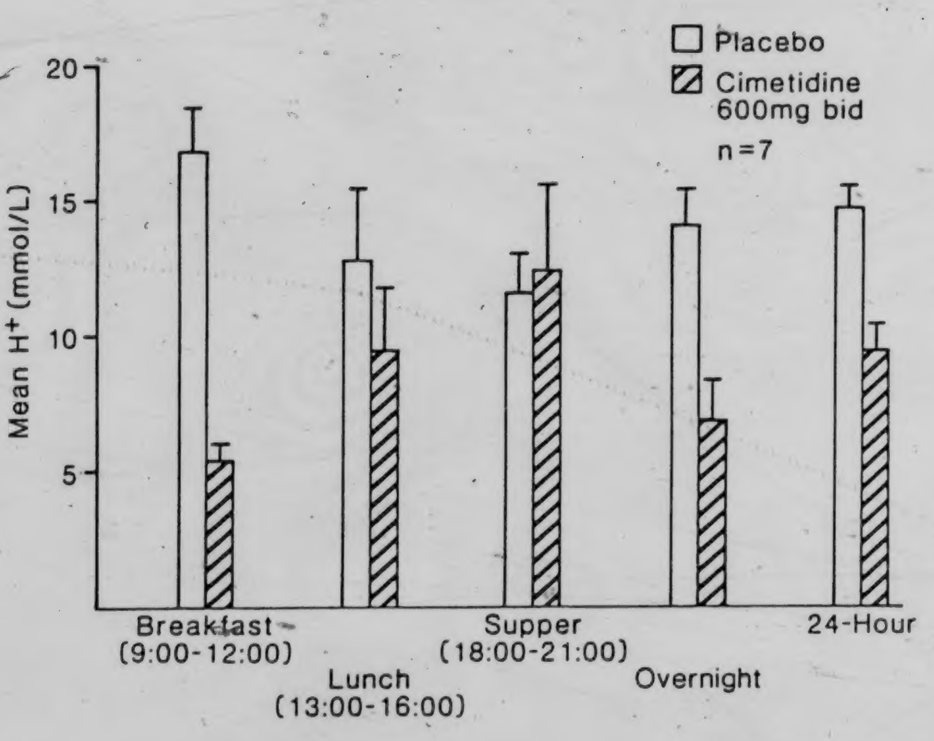

Figure 7. Mean intragastric H^+ activities after meals, overnight and over 24-hour period in normal subjects (n = 7) treated with cimetidine 600 mg bid and placebo (mmol/L), mean ± SEM

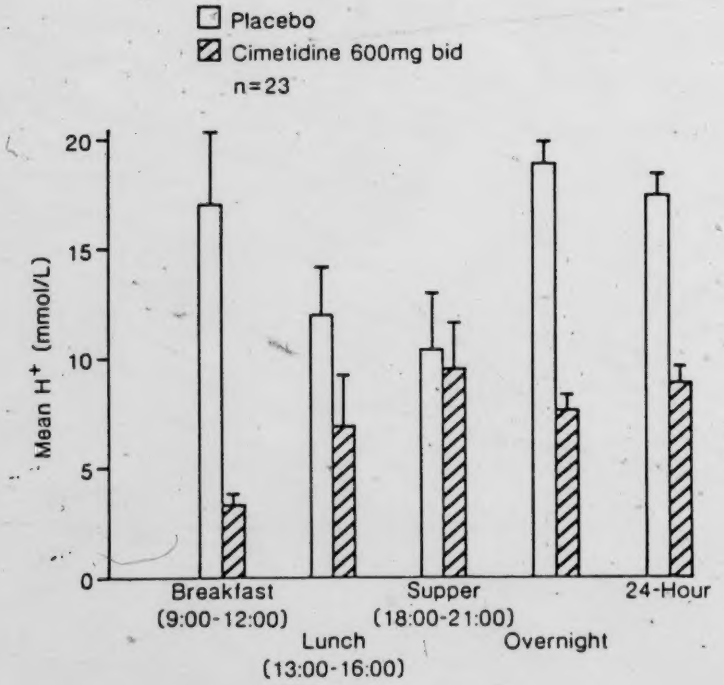

Figure 8. Mean intragastric H^+ activities after meals, overnight and over 24-hour period in duodenal ulcer patients (n = 23) treated with cimetidine 600 mg bid and placebo (mmol/L), mean ± SEM

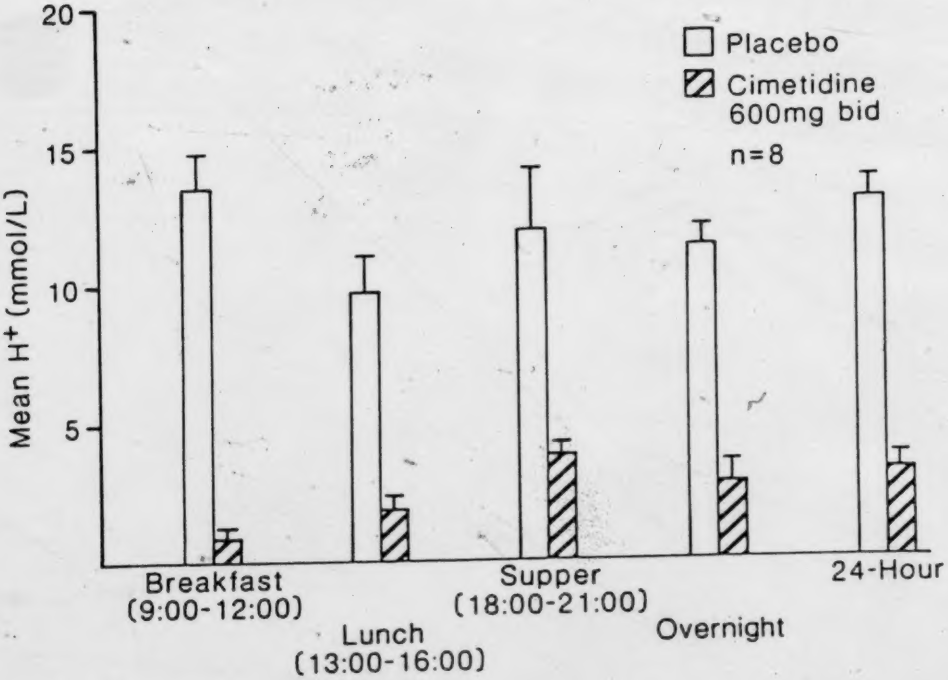

Figure 9. Mean intragastric H^+ activities after meals, overnight and over 24-hour period in patients with gastric ulcer (n = 8) treated with cimetidine 600 mg bid and placebo (mmol/L), mean ± SEM

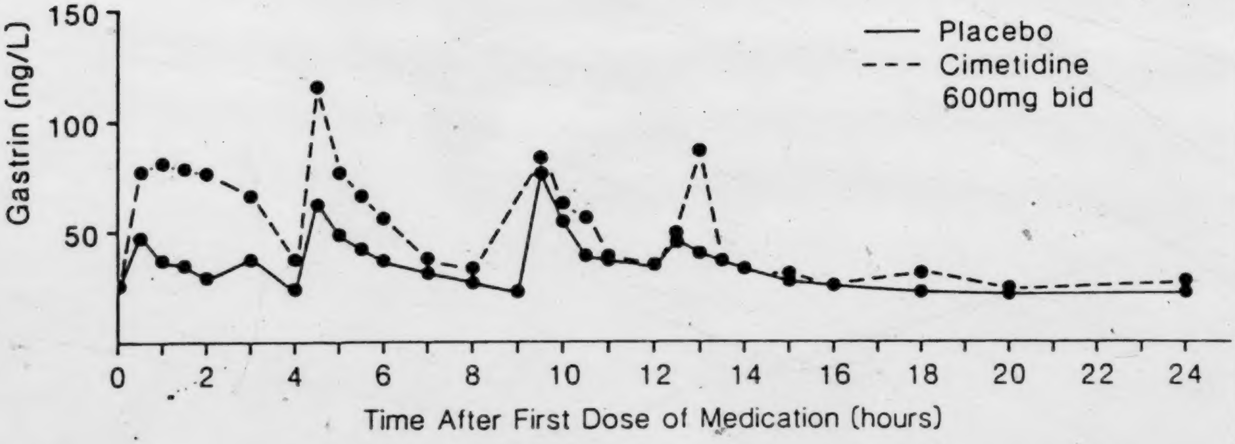

Figure 10. Mean serum gastrin concentration over 24-hour period in normal subjects (n = 7) treated with cimetidine 600 mg bid and placebo (ng/L).

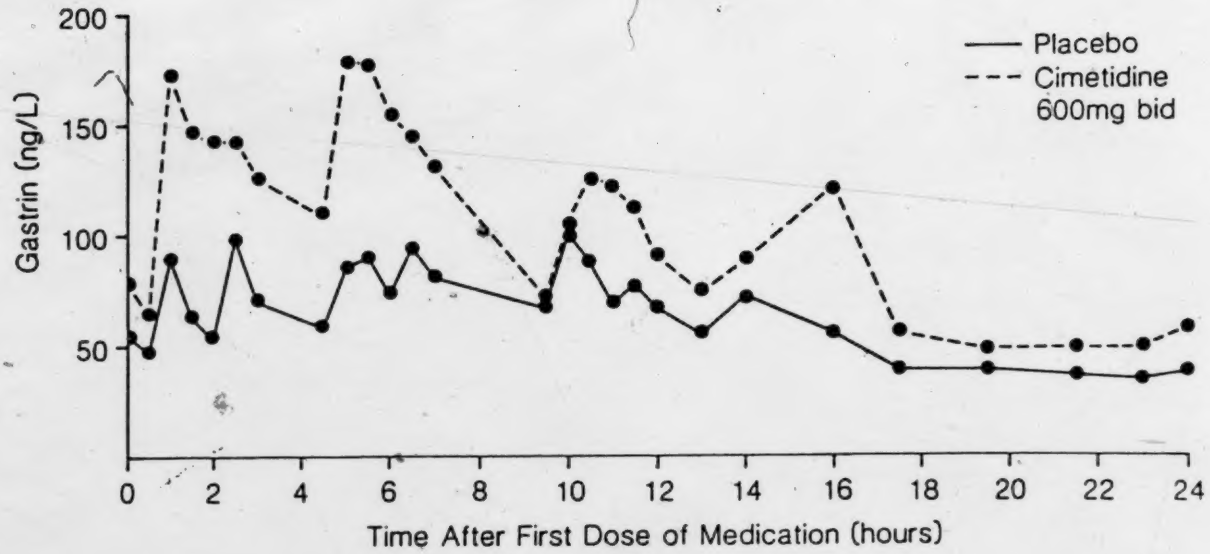

Figure 11. Mean serum gastrin concentration over 24-hour period in duodenal ulcer patients (n = 23) treated with cimetidine 600 mg bid and placebo (ng/L)

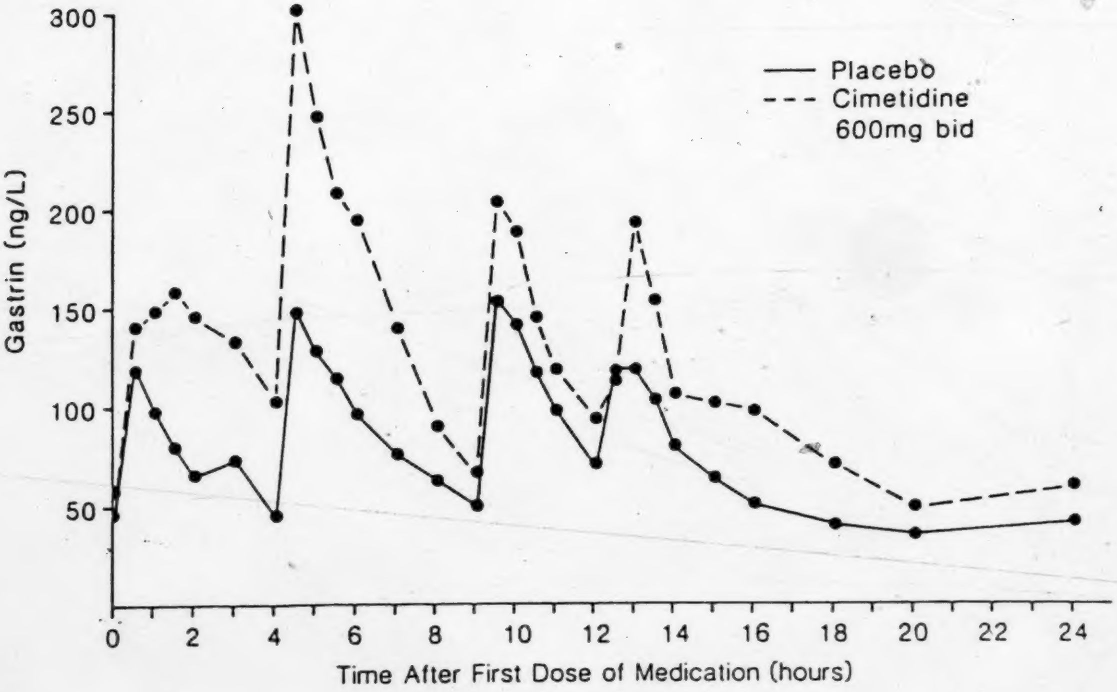

Figure 12. Mean serum gastrin concentration over 24-hour period in patients with gastric ulcer (n = 8) treated with cimetidine 600 mg bid and placebo (ng/L)

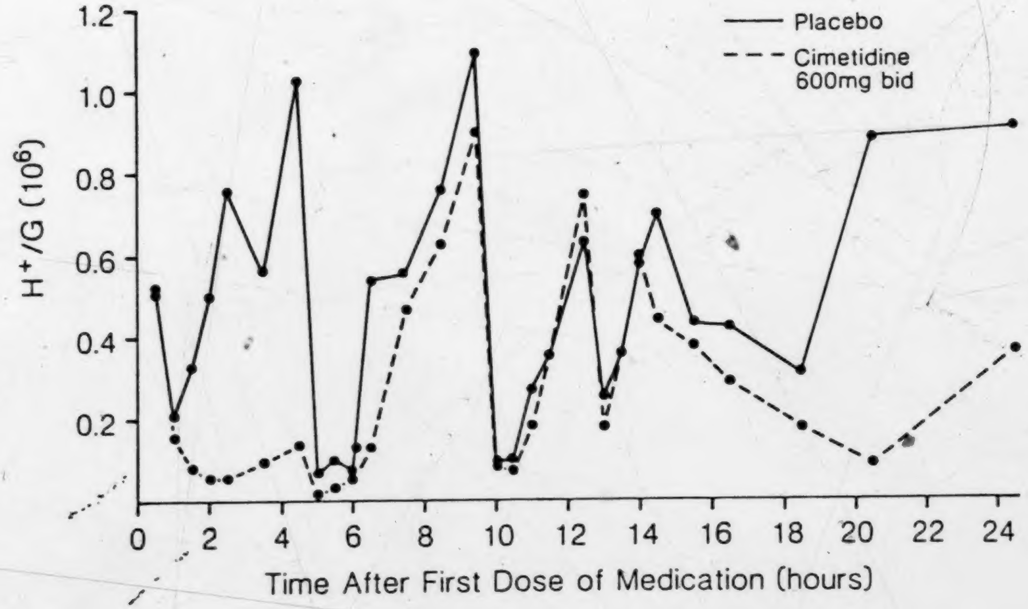

Figure 13. Mean ratio of H^+ activities and gastrin concentration (H^+/G) over 24-hour period in normal subjects (n = 7) treated with cimetidine 600 mg bid and placebo

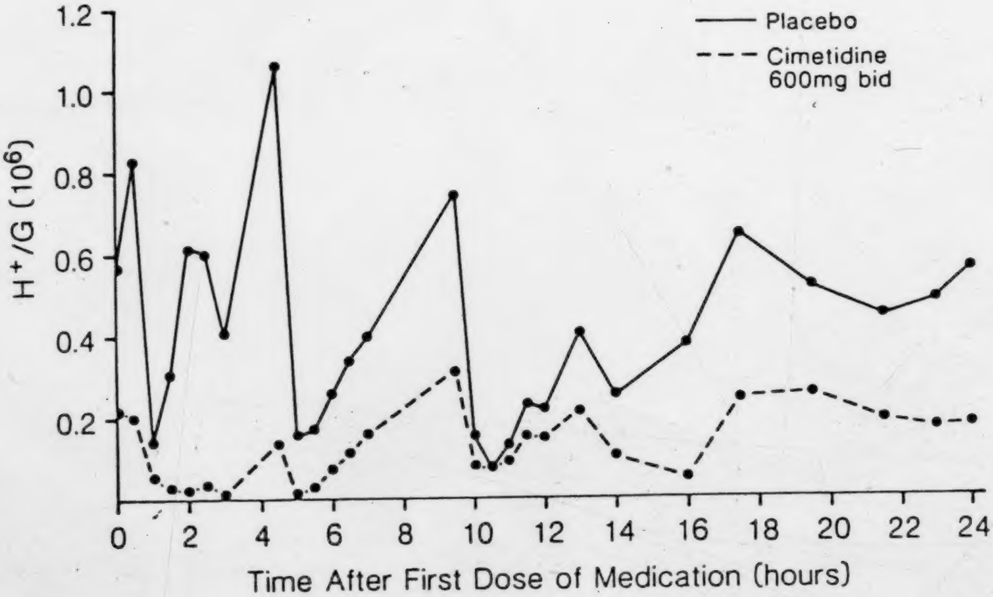

Figure 14. Mean ratio of H^+ activities and gastrin concentration (H^+/G) over 24-hour period in duodenal ulcer patients (n = 23) treated with cimetidine 600 mg bid and placebo

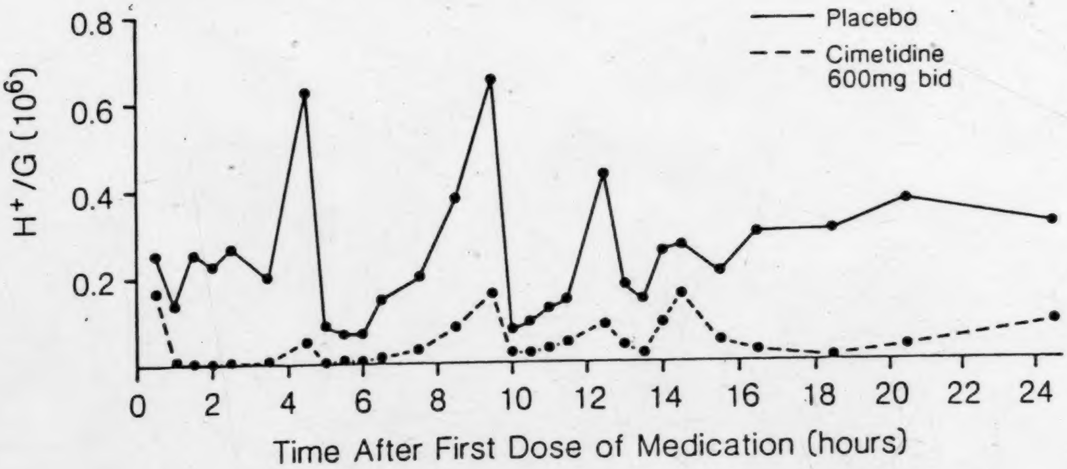

Figure 15. Mean ratio of H^+ activities and gastrin concentration (H^+/G) over 24-hour period in gastric ulcer patients (n = 8) treated with cimetidine 600 mg bid and placebo

9. SUMMARIZING DISCUSSION

The series of studies presented is the result of an attempt to elucidate and unify the various physiological aspects in both normal subjects and peptic ulcer patients. The results provide a better understanding of normal gastric physiology in the aspects of gastric acidity and gastrin profile and altered physiological responses occurring in the acid-peptic diseases. The studies also demonstrated the pharmacological effects of various antisecretory agents on intragastric acidity and serum gastrin concentration. These may provide a rationale basis for a better approach to the treatment of peptic ulcer disease. The role of gastric acid in duodenal ulcer disease is generally accepted but the role of gastric acid in gastric ulcer and gastroesophageal reflux disease is still controversial. However, the treatment of these conditions has been directed at gastric acid reduction.

Previous literature suggested that patients with duodenal ulcer tend to have higher BAO and MAO than those in normal subjects[44]. Both BAO and MAO are the measurements of both acid volume and concentration in the absence and in the presence of exogenous stimuli. We believe that acid concentration may be important in the pathogenesis of peptic ulcer disease as it reflects the amount of H^+ present at the mucosal membrane available for damage. Therefore we have studied the intragastric H^+ activity over a prolonged period under physiologic conditions in normal subjects and in patients with acid-pepsin disorders.

We selected to study the effects of various antisecretory agents which have different mechanisms on gastric acid inhibition based on parietal cell function. We have studied the effect of a commonly used H_2-receptor antagonist, cimetidine, in normal subjects and patients with duodenal or gastric ulcer. The effects of two H_2-receptor antagonists, cimetidine and ranitidine, were tested in patients with a past history of reflux esophagitis. Some patients with peptic ulcer disease fail to respond to a single agent. One of the reasons of this failure to respond to a single agent therapy may be an inadequate suppression of gastric acid. Accordingly, we have evaluated the effects of combination of H_2-receptor antagonist and acid neutralizing agent or antimuscarinic agent. Prostaglandin analogues inhibit gastric acid secretion by blocking the release of c-AMP [111]. The effects of different doses of Enprostil, a synthetic prostaglandin, were also compared with cimetidine in patients with duodenal ulcer.

Mucosal damage is believed to occur when the aggressive factors of acid and pepsin overwhelm the mucosal defense mechanisms. Studies on the pathophysiologic mechanisms of the diseases so far have mainly focused on potentially aggressive factors, particularly on gastric acid. There has been increasing knowledge on the role of mucosal defense mechanisms in protecting gastric mucosal injury, as suggested by studies using agents such as prostaglandins and carbenoxolone that enhance mucosal defense by different mechanisms. The pathophysiologic role of mucosal defense in peptic ulcer disease is not yet known.

A 24-hour pH monitoring has been a useful technique for evaluating the pharmacological effects of antisecretory agents and the choice of the optimum dosage regimen in duodenal ulcer patients[70,72] and in normal subjects[73]. Clinical responses to antisecretory agents in patients with the Zollinger-Ellison syndrome have been shown to correlate with their effect on the 24-hour intragastric acidity[105]. By using this technique, the effect of diet and drugs can be tested over a prolonged period under the physiologic conditions closest to real life in which the medications are to be used. The study of intragastric acidity in patients with duodenal ulcer disease is potentially relevant to the pathogenesis of the disease as there is a close correlation between the acidity in the stomach and the acidity present in the first part of the duodenum[3]. Under the controlled test conditions used in this study, standardized meals were provided and the number of cigarettes consumed and the volume of intake were controlled. All subjects received standardized meals, as the buffering capacity of food is influenced by the quantity and the nature of food[5,58]. The reproducibility of the method was assessed in seven duodenal ulcer subjects who repeated the study on separate occasions under similar conditions while receiving placebo and identical meals with comparable amounts of fat, carbohydrate and protein. The mean correlation coefficient between the results from two sets of 24-hour intragastric pH recordings in duodenal ulcer patients was 0.17 ($p<0.05$).

With this experimental technique, we were unable to determine the total volume of gastric content over the 24-hour period. It is not certain whether acid concentration or acid volume is more important in the formation of peptic ulcer. Gastric acid concentration may determine the amount of H^+ at the mucosal surface which may be damaging to the gastric mucosa. Cimetidine was shown to have an effect on both nocturnal acid secretory volume and total acid output in duodenal ulcer subjects. We assumed that cimetidine would similarly have an effect on both H^+ activities and acid secretory volume throughout the 24-hour period. We chose to measure the H^+ activities as determined by pH measurements, as it was felt to be a useful measurement to determine the effects of various antisecretory agents on gastric acidity. The relationship between the levels of acid secretion and the adverse effect of the development of peptic ulcer disease is not known. It is not certain which of the measures of acid secretion best describes the pathophysiologic role of gastric acid. The critical time that gastric acid needs to be suppressed is not known. Our studies suggested a diurnal variation of acid secretion, with the highest concentration after breakfast and during the night in all patient groups and in normal subjects.

The results of these studies failed to confirm the discrepancies between the 24-hour gastric acidity as expressed in pH or H^+ activities in patients with inactive duodenal ulcer, gastric ulcer and normal subjects. Only subjects with duodenal ulcer tended to have higher basal acid output and stimulated acid output in response to exogenous pentagastrin as compared to normal subjects. However, there were considerable overlaps of these values in duodenal ulcer patients and normal subjects. This wide range of BAO or MAO in duodenal ulcer patients suggested a different spectrum of acid secretion in this group of patients. The BAO and MAO tended to be lower in gastric ulcer patients than in normal subjects with considerable overlaps. However, the MAO was significantly lower in gastric ulcer patients than in duodenal ulcer patients.

Gastroesophageal reflux disease is not generally thought of as acid-pepsin disorder. Mechanical factors seem to be more important in the pathogenesis of the disease. However, both acid and pepsin have been shown to be damaging to the esophageal mucosa[33,39]. One of the mainstays of therapy of this disease is gastric acid reduction. We were unable to confirm the findings of others who suggested that BAO was higher in patients with gastroesophageal reflux disease than normal controls[7]. The study showed similar BAO and MAO in this group of patients who had previous history of esophagitis as compared to normal subjects. We found that gastric content in this patient group was highly acidic with 90% of the pH readings < 4.0. Their 24 hour pH profile or H^+ activity was not different than that of normal subjects.

These studies were carried out in patients with inactive DU, GU and GERD. It is not known whether the acid secretion changes with disease activity. A previous study showed that acid secretion was higher in patients with active DU than in healthy controls or in patients with inactive DU[1]. We speculate that the altered acid secretion may not be a primary defect in any of these conditions, although it may increase the propensity of mucosal damage or ulceration. The reduction of gastric acid by antisecretory agents may only decrease the damaging effect of other agents such as pepsin or bile. Peptic activity increases in the presence of acid[71]. The altered pepsin secretion in peptic ulcer disease has not been fully studied but such studies are currently intensively examined by others.

A previous study suggested that there is a higher basal gastrin concentration in patients with gastroesphageal reflux disease[84]. Our study did not show any difference in either basal gastrin concentration or gastrin response to food between the patients with a previous history of esophagitis and normal subjects. The gastrin response to food tends to be higher in both duodenal and gastric ulcer patients than in normal subjects. The higher gastrin response to food may be caused by any one factor or a combination of several factors including: increased numbers of G-cells, increased sensitivity of G-cells, defective feedback control mechanism of acid on gastrin release, prolonged G-cell stimulation by intraluminal nutrients or gastric distention. The higher gastrin response to food in DU and GU may be operating through different mechanisms. The molecular forms of G-17 and G-34 of serum gastrin concentration were not measured in this study. It was previously thought that circulating G-17 is five to six times more potent than G-34 in stimulating acid secretion but is metabolized more rapidly than G-34 [107]. Recently, it was suggested that G-34 and G-17 have a similar potency[23]. The higher H^+:G ratio in normal subjects than in patients with DU and GU suggested a lower sensitivity of acid secretion to endogenous gastrin in the DU and GU patients. This does not correspond to the higher sensitivity to exogenous gastrin in DU patients as shown in this study or in the others[44]. This may also represent a defective feedback control of gastric acid on gastrin release in these patients with DU or GU.

Cimetidine 600 mg bid suppressed intragastric H^+ after breakfast and during the night in DU patients and in normal subjects, whereas H^+ suppression was obtained after all meals and during the night with the same dosing regimen of cimetidine in GU patients. Thus these GU patients appear to be more sensitive to the inhibitory effects of cimetidine. The meal-stimulated gastrin response was enhanced by cimetidine to a greater extent in DU or GU than in normal subjects. The ratio of H^+:G was markedly suppressed by cimetidine in DU and GU patients but was minimally suppressed by cimetidine in normal subjects. The differences in meal-stimulated gastrin response and the ratio of H^+:G between normal subjects and patients with DU or GU were accentuated by cimetidine. This result suggests that the sensitivity of H^+ to gastrin may be altered by cimetidine in both groups of patients with acid-pepsin disorders.

For the purpose of patient compliance, the dosing regimen of cimetidine was modified to 600 mg twice a day. The results suggested that this dosage regimen of cimetidine is superior to the standard regimen of cimetidine 300 mg qid in suppressing H^+ activities after breakfast and during the night. This superiority cannot be explained by the change in gastrin concentration or by the difference in serum cimetidine concentration. Similar pharmacokinetics were obtained with cimetidine 600 mg bid and cimetidine 300 mg qid, and there was no correlation between the serum cimetidine concentration and acid suppression. It is possible that acid inhibitory action of cimetidine may be a local effect on the parietal cells. The serum gastrin response to food was enhanced similarly in both cimetidine-treated groups.

Both cimetidine and ranitidine suppressed intragastric H^+ activities after breakfast and during the night in patients with a past history of reflux esophagitis. In these patients, the gastric content was highly acidic, with 90% of the pH readings remaining at or above 4.0. In these patients, ranitidine given as 150 mg bid was superior to cimetidine 300 mg qid in suppressing the mean intragastric H^+ activity after lunch. Thus, even when using doses of the two H_2-receptor antagonists which are commonly used therapeutically for ulcer healing, ranitidine is a more potent antisecretory agent than cimetidine.

The combination of cimetidine twice a day and frequent antacid, administered one and three hours after meals, markedly suppressed intragastric H^+ activities during the day and at night. Antacid alone given one and three hours after meals and at night maintained the acid neutralizing effect during the day but only had an effect during the early hours of the night shortly after the nighttime dose. Less frequent doses of antacid given four times a day, one and three hours after lunch and supper, maintained the acid neutralizing effect during this time when combined with twice a day cimetidine. Thus, it appears that lower H^+ activity can be obtained with a combination of antacid and cimetidine, than with either cimetidine or antacid alone. It remains unknown whether this greater neutralizing and antisecretory effect has any therapeutic value.

The effect of the selective anti-muscarinic agent, pirenzepine, either alone or in combination with cimetdine, was compared to cimetidine 600 mg bid. Pirenzepine 50 mg bid by itself failed to suppress intragastric H^+ activities or nocturnal acid volume or total acid output. This study failed to demonstrate a possible role of increased vagal activity in this group of DU patients as they should theoretically respond to this antimuscarinic agent. However, we did not study patients who had failed to heal their DU with a previous course of treatment with an H_2-receptor antagonist. When pirenzepine 50 mg bid was combined with twice a day cimetidine, a more prolonged acid suppression was observed after lunch, as compared to cimetidine alone. Both combination therapy and cimetidine alone suppressed nocturnal acid volume, acid concentration and total acid output. Combination therapy tended to suppress both nocturnal acid secretory volume and acid output for a longer period, as compared to cimetidine alone. Thus the combination of pirenzepine and cimetidine may be of therapeutic benefit in DU patients, particularly in those with nighttime symptoms due to acid secretion at this time, or in those patients who have failed to heal with single agent therapy, including cimetidine.

Enprostil, a synthetic prostaglandin E_2, increases intragastric pH in a dose dependent manner. Enprostil 35 mcg bid is at least as effective as cimetidine 600 mg bid in suppressing intragastric H^+ both during the day and during the night. A single nighttime dose of Enprostil 70 mcg was associated with a similar degree of nocturnal H^+ activity suppression as compared with Enprostil 35 mcg bid. The reason for this "carry-over" effect of the twice daily regimen is unclear.

The serum gastrin concentration in response to food was enhanced by all medications that suppressed intragastric H^+ activity. The only exception was that the gastrin response after breakfast was markedly blunted by Enprostil 35 mcg bid, and the gastrin responses after supper were lower in all Enprostil regimens as compared to cimetidine treatment in spite of similar H^+ activity suppression after the nighttime doses. This suggested that Enprostil may inhibit gastrin release in addition to its effect on suppressing acid secretion by the parietal cells. The mechanism of this gastrin inhibition is unknown. Neither is it clear why this antigastrin effect was so prominent after breakfast. The higher gastrin responses to food in other antisecretory regimens may be due to the lack of negative feedback of intragastric acid on gastrin release. However, the ratio of H^+ and gastrin concentration markedly fluctuated in all subject groups without a close correlation between the two measurements. This suggests that the releases of H^+ and gastrin also depend on other factors.

The pharmacokinetic study showed a diurnal variation of cimetidine given as 600 mg bid, with a higher peak concentration and a greater area under the curve after the morning dose than after the evening dose. We do not have the explanation for this diurnal variation of cimetidine pharmacokinetics. Further study has been attempted to determine if this observation is due to a diurnal physiologic mechanism of absorption of this drug. A similar observation was obtained when the antimuscarinic agent, pirenzepine, was combined with cimetidine (Mahachai V, et al, unpublished observations, 1984). This antimuscarinic agent did not interfere with cimetidine pharmacokinetics (Mahachai V, et al, unpublished observations, 1984). Thus the diurnal variation in the pharmacokinetics of cimetidine is unlikely to be due to cholinergic-mediated factors.

A similar cimetidine profile was obtained when cimetidine 600 mg bid was combined with antacid seven or four times a day. We failed to support the previous finding[95] that concomitant administration of antacid interferes with the absorption of cimetidine.

In spite of the effectiveness of all groups of antisecretory agents in gastric acid suppression and even in the healing of peptic ulcer disease, the etiologic role of gastric acid in these diseases was not confirmed. We may be indirectly treating acid-peptic disease by the reduction of acid. Gastric acid may only play a permissive role in the disease formation. In order to alter the natural history of the disease, the primary defect should first be determined and corrected. This primary defect may not necessarily be represented by defects in acid secretion[113]. Thus, the studies reported here give some basis for the selection of therapeutic regimens in the treatment of acid-pepsin disorders, and indeed for the optimization of this therapy, but these studies do not explain the cause of duodenal or gastric ulcers.

10. RECOMMENDATIONS FOR FUTURE RESEARCH

Future studies are needed to define different subgroups of peptic ulcer patients who may possess different pathophysiologic mechanisms of the disease. For example, studies of acid secretion should be performed in patients who fail to heal their ulcer with H_2-receptor antagonists. The altered mucosal defense and pepsin metabolism need to be further defined in these patients. Acid hypersecretion may still be important in a certain subgroup of patients. For example, the suggestion that the normal increase in mucosal prostaglandin levels in response to acid in the duodenum is defective in DU (2) needs to be confirmed. Indeed, acid may only be a permissive marker for the development of ulcer disease. This subgroup of patients will certainly benefit from potent antisecretory regimen. The new strategy of treating peptic ulcer disease by utilizing agents that improve mucosal resistance or inhibit peptic activity should be further investigated.

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12. APPENDIX

MEDICAL MANAGEMENT OF UNCOMPLICATED PEPTIC ULCER DISEASE IN ADULTS

(A slightly modified version of this chapter has been submitted for publication in Bockus Textbook of Gastroenterology, 1984, A.B.R. Thomson and V. Mahachai)

Peptic ulcer disease is a common medical problem which results in considerable morbidity and mortality due to its propensity for recurrences and the development of hemorrhage, obstruction and perforation. It is debatable whether duodenal and gastric ulcer disease are separate entities, or different manifestations of the same process. This process of ulcer formation is associated with numerous pathophysiological abnormalities related to excess aggressive and inadequate defensive factors, but it is unclear whether these changes are of etiological significance.

General Principles

In the total assessment of the patient with peptic ulcer disease, it is helpful to enquire about their lifestyle, including the nature and hours of work, habits of eating, sleeping, smoking and drinking, their worries and concerns, their sources of relaxation and pleasure, their hopes and aspirations. Enquire about the use of drugs, especially previous use of and possible benefit from antacids, anticholinergics, and H_2 blockers or cytoprotective agents. Most importantly, ask about the patient's use of aspirin or other over-the-counter drugs which may contain non-steroidal anti-inflammatory agents (NSAIA).

In the management of the patient with a peptic ulcer, do not lose sight of the importance of the patient-physician relationship. The personality of the physician, his/her sympathy and understanding of the patient, and the patient's interpersonal relationships and current life situation are all important. At a time when we question whether the healing of ulcers is due to potent new anti-ulcer medications, or the glass of water used to consume the pills, it may seem foreign to some readers that this very empathy and caring demonstrated by the laying on of hands and the listening ear of the physician may provide the until recently unmatchable so-called "placebo" effect of healing of the hole in the lining of the stomach or duodenum. "When the patient realizes that the physician has a sympathetic and understanding appreciation of his problems, he(she) is more likely to accept graciously the advice which is offered relative to a readjustment of the various mental-environmental situations responsible in some measure for his illness" (66).

In our world of the mid-80's, we may sometimes act as if the old should be discarded, not cherished, and the new alone is effective. Yet, caring and compassion must continue to play a major role in the care of these patients with chronic recurrent disease. Three general rules must prevail in our approach to a problem which at some point in the life of North Americans will affect about 10% of males and 5% of females:

1. no acid, no ulcer - at least, not usually
2. once an ulcer, always an ulcer - as long as the original diagnosis was correct
3. not all dyspepsia is from an ulcer.

Let us examine each of these guiding principles.

No Acid, No Ulcer

There are demographic and psychological characteristics which may or may not typify the usual patient with peptic ulcer disease. There are numerous pathophysiological disturbances present in at least some patients with these gastric or duodenal lesions. This development of an ulcer represents an imbalance between aggressive and defensive factors in the upper gastrointestinal tract. The aggressive factors relate to the presence of acid and pepsin in the gastric lumen or at the interface of the membrane and the luminal contents. The acid and pepsin are released for the purpose of beginning the digestion of food, and not for the digestion of the gastric or duodenal mucosa! Peptic ulcer disease is a heterogeneous group of disorders (448-450) with variable severity (149), and it would be incorrect to assume that the presence of excessive acid and pepsin necessarily represent etiological mechanisms (557). Some of these abnormalities may even prove to be the result rather than the cause of the disease (Table 1). Some of these disturbances may even be defensive, the body's attempt to achieve normal mucosal repair. Since peptic ulcer disease is most probably heterogeneous in etiology, as evident clinically (289,290,447), genetically (288,449,451), and pathophysiologically (197,284), no single factor is likely to discriminate ulcers that heal - or recur - or fail to heal - from those that do not. It would be helpful in the selection of therapy for a given patient, for the more optimal design of clinical trials, and for the better understanding of the basis of ulcer disease, to know what factors influence ulcer healing.

Table 1

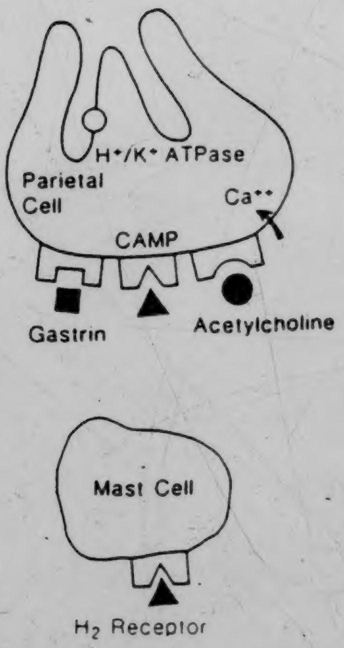
PATHOPHYSIOLOGICAL ABNORMALITIES IN DUODENAL ULCERATION

There is evidence for/against these abnormalities being of etiological significance

1. Increased Parietal Cell Mass
2. Increased Sensitivity of Parietal Cells to Stimuli
3. Increased Stimulation of Parietal Cells by Increased Circulating Gastrin
4. Decreased Sensitivity of Parietal Cells to Inhibitory Factors
5. Increased Numbers of Antral G-cells
6. Reduced Acid-Inhibition of Gastrin Release
7. Increased Secretion of Gastric Juice
8. Rapid Emptying of Gastric Contents
9. Decreased Acid-Stimulated Release of Secretin From Small Intestine
10. Increased Threshold for Secretin Release
11. Decreased Secretion of Pancreatic Bicarbonate
12. Increased Acidity in Duodenal Bulb
13. Impaired Acid-Stimulated Duodenal Mucosal Synthesis of PG's

Let us consider the parietal cell and its role in the secretion of acid (Figure 1). H_2 antagonists and anticholinergic agents inhibit even basal acid secretion. This suggests that in the basal state the parietal cell is under both histaminic and cholinergic "tone". Several lines of evidence indicate that the isolated canine parietal cell possesses specific receptors for histamine, acetylcholine, and for gastrin (488-495). Gastrin appears to directly stimulate the canine parietal cell by interacting with a specific receptor closely related to CCK (253). A three-way interaction may occur among histamine, carbachol and gastrin (44). The second messengers for the secretagogue action include cyclic AMP and calcium. Histamine stimulates cAMP production by parietal cells (98,495), whereas this is not the case for gastrin or carbachol. Cholinergic stimulation of parietal cell function is coupled to the enhanced influx of extracellular calcium (489). Stimulation of secretion by gastrin was not associated with calcium influx.

Prostaglandin of the E_2 series inhibits cAMP production by isolated canine parietal cells, and by blocking histamine stimulation of parietal cell function, but does not inhibit the effects of either carbachol or gastrin (488,491). Histamine stimulation of cAMP is also inhibited by prostaglandins (491). Lanthanum, which blocks calcium fluxes across plasma membranes, inhibits cholinergic stimulation of parietal cell function. Atropine and H_2-receptor antagonists block gastrin-stimulated acid secretion by removing the potentiating effects of acetylcholine and histamine, respectively. Prostaglandin blocks cAMP formation, which is necessary for histamine to stimulate acid secretion. Thus prostaglandin eliminates the interaction between gastrin and histamine. Neither atropine nor metiamide alters the binding of gastrin to its receptor (519).


H+/K+ ATPase
Parietal Cell
Ca++
CAMP
Gastrin
Acetylcholine
Mast Cell
H2 Receptor

Function	Inhibitor
Proton Pump	Omeprazole
Cell Activation	Calcium Channel Antagonists ie. Verapamil Prostaglandin
Receptors	H_2 Blocker Cimetidine Ranitidine Acetylcholine Muscarinic Blocker Non-selective ie. Atropine Selective ie Pirenzepine Gastrin Blocker Proglumide

Figure 1: Classification of Inhibitors of Parietal Cell Function

We need to know which of the many measures of acid secretion best describes the pathophysiologic role of acid: basal or stimluated secretion, and stimulated with what- food, sham feeding, histamine or pentagastrin? And is the critical factor for mucosal damage acid concentration, volume or output? Is it a matter of time and acid concentration, i.e. the area under the acid-output curve? Is it the acid present in the stomach which is important in duodenal ulcer disease, or more likely the acid present in the duodenal bulb? Is it the amount of acid after meals which must be suppressed or the acid present overnight? Why do ulcers commonly occur in the duodenal bulb, pyloric channel or gastric antrum? Why do they tend to recur at the same site? Is there a single insult, or many small events which culminate in an ulcer? These questions are currently unanswered.

True, some patients with duodenal ulcers may secrete excessive volumes of hydrochloric acid. Some patients with gastric ulcers may secrete normal rather than low amounts of acid (199,559) and there is considerable overlap in the individual values within patient groups. However, the 24-hour intragastric pH is similar in asymptomatic normal volunteers, gastric ulcer (GU) and duodenal ulcer (DU) patients (332). An ulcer likely begins as a defect in the mucosa i.e. an erosion, which later extends beyond the muscularis mucosa to form an ulcer. However, initially the concentration of acid at a given point in the membrane is no different in health and disease. Indeed, if a biopsy is taken at the time of endoscopy in a patient with a duodenal ulcer, the mucosa quickly heals. A chronic ulcer does not form, possibly because the mucosal defense and repair mechanisms are intact. The propensity for the MAO to decline in DU patients after ulcer healing raises the prospect that the elevation of hydrochloric acid volumes or secretory rates may be, at least in part, the result and not solely the cause of ulceration. Nonetheless, even if acid only plays a permissive role, most clinical scientists would support the time-honoured dogma of "no acid, no ulcer". Regardless of the role that anxiety and frustration may play in enhancing acid secretion, or more importantly, in heightening the symptomatic response to the ulcer pain, acid must play some leading role in this drama of gastric and duodenal ulceration.

Once an Ulcer, Always an Ulcer

Gastric ulcers, like duodenal ulcers, tend to recur (208). Benign recurrent ulcers may heal as readily as did the index ulcer (315). If malignant degeneration of a previously benign gastric ulcer does occur, it must be rare (343). To the patient, it is important to avoid recurrent bouts of pain, and serious ulcer-related complications such as bleeding, perforation, or gastric outlet obstruction. But ulcers come and go, and in view of the repeated observation that about one patient in three will have an asymptomatic recurrence of ulcer per year, then these patients likely have many unnoticed recurrences over their lifespan. We do not yet know whether preventing the asymptomatic - as well as the symptomatic - recurrences does in fact prevent the development of major complications. Indeed, most experienced clinicians have seen DU patients present with an upper gastrointestinal hemorrhage while they are on maintenance anti-ulcer therapy.

The cause or causes of peptic ulcer are not known, nor have the causes of ulcer relapse been established. Factors leading up to the initial development of the disease may not be the same as those leading to a relapse. Early relapse after healing may be associated with high acid output (458,510). Several studies reported more relapses in the patients with a longer history of disease (26,145,200,338,344,458,459,510), or with smoking (496). In one study, ulcer recurrence was more common in patients using a low fiber diet (462). Thus, in this era of fast foods, quick riches and instant everything, the patient may expect and demand rapid relief of pain and a permanent cure of the ulcer. Just as factors in life-style must be stressed, so also is it important for the physician to emphasize to the patient that the ulcer will recur, not through some shameful defect in the patient or the physician, but rather simply because that's the way it is - in most patients, ulcers recur. Equally, the patient must be reassured that each episode of pain may be successfully treated, that the risk of complications may be relatively small, and that there is a promise that the natural history of the ulcers to recur may be modified somewhat by exercising acceptance of some prudent, albeit not totally proven measures (Table 2) as well as by taking effective maintenance medications.

A small proportion of patients may suffer only a single attack of symptomatic ulceration, but most patients with a duodenal or gastric ulcer will relapse, with an annual recurrence rate of about 75% (417) and a 10-year risk of potentially serious complications (bleeding requiring a transfusion, perforation or obstruction) of 11% (149) and a 20% life-long risk of complications (69). Complication rates were about 2.7% per year for those with no prior complication, and about 5% per year for those with a prior complication. Thus, stress the positive to the patient: an ulcer program is intended to relieve symptoms, heal the ulcer, and thereby prevent complications. No, ulcer programs do not cure the ulcer disease, do not permanently alter the natural history of the disease, but only heal the ulcer at one point in time.

Table 2

FACTORS POSSIBLY IMPORTANT IN ULCER RECURRENCE

1. SMOKING
2. LONG PAST HISTORY
3. HIGH ACID OUTPUT
4. LOW FIBER DIET

Not all Dyspepsia is From an Ulcer

It should be recognized that there are as many causes of chronic recurrent food-related epigastric pain (357,371) as there are definitions of dyspepsia (528). While certain characteristics of the pain may suggest ulcer disease (Table 3), it must be stressed that about half of patients with dyspepsia will have an ulcer (193,203,221,551), and half of patients with an ulcer will have dyspepsia (371,425).

Table 3

COMMON CHARACTERISTICS OF PAIN DUE TO PEPTIC ULCER

1. USUALLY LAST ONLY A FEW HOURS
2. TEND TO OCCUR DAILY FOR SEVERAL DAYS, WITH FREEDOM FROM SEVERE SYMPTOMS FOR SEVERAL WEEKS OR MONTHS
3. ARE FREQUENTLY NOCTURNAL
4. ARE OFTEN RELIEVED BY ANTACIDS

The most common functional overlay in the patient with ulcer disease is aerophagy. Persisting epigastric pain plus anorexia and weight loss should raise the concern of the presence of gastric cancer. Thus, each recurrence of symptoms in a patient with a long past history of acid-pepsin disease must be reassessed as to its nature and basis.

It must be recognized that duodenal and gastric ulcers often heal within a month without the addition of therapeutic agents. These placebo-healing rates vary widely, from 0% in Italy to 79% in U.S.A. and West Germany (131). These differences from country to country and from study to study within a country may be influenced by demographic, life-style and physiological factors which might affect ulcer healing and recurrence. Also, study design may influence placebo healing rates, such as the concurrent use of antacids or non-steroidal anti-inflammatory agents, and the different criteria used for definition of healing.

The prognosticators for ulcer healing are shown in Table 4. Past attempts to identify the healing factors can be criticized as not composite and comprehensive in approach (285). The adverse effect of cigarette smoking is generally accepted; acid secretion, sex and age have been controversial; and alcohol appears to be possibly unfavourable. In the discriminant analysis of Lam and Koo (285), individual analysis using stringent statistical criteria identified only two pertinent factors: cigarette smoking, including the quantity of cigarettes consumed, and ulcer size, both their diameter and depth. Two acid-related physiological measurements were identified to be of discriminant value in cimetidine-treated patients; these were the fasting serum gastrin concentration and the D_{50} of the pentagastrin dose-response test, which measures the parietal cell sensitivity to pentagastrin.

Table 4

PROGNOSTICATORS OF ULCER HEALING

1. MALE SEX (32,340,344,348,374,377,405,408,496,548)
2. SMOKING (242,287,348,496)
3. LONG PAST HISTORY
   longer history of ulcer (32,55,287,338,340,374,377)
4. SEVERE PAIN (348)
5. ACID HYPERSECRETION (either BAO or MAO)
   (55,222,287,348,408)
6. ULCER SIZE (285)
7. FASTING GASTRIN CONCENTRATION (285)
8. D_{50} OF PENTAGASTRIN DOSE RESPONSE (285)
9. ALCOHOL CONSUMPTION (285)
10. BACK PAIN (285)
11. PAST HISTORY OF BLEEDING (285)

Curiously, the lower the fasting serum gastrin concentration, and the more sensitive the patient is to pentagastrin, the smaller is the chance of healing with cimetidine treatment. This discriminant analysis also identified ulcer diameter, late onset disease and body weight, analgesic consumption and neurosis, to be of discriminant value as factors unfavourable to healing by cimetidine. In the placebo-treated group, back pain, previous gastrointestinal bleeding, and alcohol consumption were selected as factors unfavourable to healing. These possible prognosticators are important, since clinical trials do not usually randomize separately for these factors which may be associated with a poor clinical response. Secondly, the failure of a therapeutic regimen to result in healing within a given study period may relat to the uncontrolled and adversely interacting influence of one or more factors which retard the natural tendency of many patients to heal their ulcer. Finally, let us examine the potential benefit of altering the patient's life style on ulcer healing.

Prudent Approaches to Lifestyle

Let us examine the benefit of altering the patient's lifestyle on ulcer healing (Table 5).

Table 5

PRUDENT APPROACHES TO LIFE STYLE IN ULCER HEALING AND PREVENTION OF RECURRENT SYMPTOMS OR ULCERATION

1. FOOD
   - a) eat three nutritionally balanced meals a day
   - b) if pain occurs between meals and a snack helps, then welcome that help
   - c) unless a given food makes your pain worse, don't otherwise purposely avoid any food substance
   - d) unless normal-sized meals cause a bloated or full feeling, there is no special need to ritualistically consume six small meals a day
   - e) foods which seem to increase epigastric discomfort in individual patients should be avoided

2. BEVERAGES
   - a) Milk - if pain is relieved by small amounts of milk, then enjoy that relief
   - b) Coffee, tea, juices and alcohol - take in moderation and avoid only if these fluids aggravate symptoms

3. SMOKING - stop smoking if at all possible

4. ACTIVITY - a reasonable exercise program for purposes of general well-being - avoid sedatives unless clearly indicated for health-related purposes other than dyspepsia or ulcer disease.

5. DRUGS - avoid aspirin, ASA-containing drugs, NSAIA and steroids

1. FOOD

The discussion of the role of diet in the management of patients with peptic ulcer disease required over 20% of the length of the chapter devoted to this subject in the last edition of Bockus' textbook of gastroenterology (62), whereas Soll and Isenberg (494) dismissed this form of therapy in half a page in Sleisenger and Fordtran's Third Edition of Gastrointestinal Disease. There are four points to take home about diet manipulation in patients with peptic ulcer disease (Table 6):

Table 6

TAKE HOME POINTS ABOUT DIET MANIPULATION IN PATIENTS WITH PEPTIC ULCER DISEASE

DIETS:

1. do not heal ulcers
2. may improve symptoms
3. may cause adverse effects
4. may play a role in the prevention of ulcer recurrence

Distension of the gastric antrum may stimulate acid secretion, but food may buffer acid. Frequent small meals used to be advised for ulcer patients, on the rational basis that acid secretion would be stimulated more frequently but less powerfully. However, in DU patients, the intragastric pH is not influenced by meals of different sizes and protein content, taken at different times of the day (331), and the mean acidity throughout the day is similar in DU patients fed two- and four-hourly (13).

Bland diets, milk therapy, or frequent feedings do not benefit the healing of peptic ulcers (86,135,298,302,535). The bland diet may play even a lesser role in the maintenance of the nutritional well-being of the patient. An appealing diet is necessary. Take into account the patient's life-style, eating habits, and food preferences. Of more importance than the nature of the diet, is the frequency of eating. Many patients with a DU will note that consuming frequent meals provides good relief of symptoms, whereas some patients with a GU who have food-aggravated pain will note that frequent small meals are of little benefit. In addition to stimulating acid secretion (164), food does buffer acid and in fact the intragastric pH rises (i.e. the gastric contents become more alkaline) after meals and snacks (328-332). The composition of the diet - total calories, or the ratio of nitrogen/calories/fats - has little effect on the intragastric pH (303). The evidence that spicy food stimulates excess acid secretion is inconclusive (463,467).

Just as some older major reviews of the management of peptic ulcer disease have stressed the importance of diet in the treatment of ulcer disease, some older patients will consider their physician to be remiss if a diet is not prescribed. Indeed, some patients will have noted that certain foods aggravate their dyspepsia. Consider such foods as coffee, alcohol, pop, orange juice, spicy foods, chocolate, and fatty foods. But surely these patients are teaching us a lesson in physiology. Foods in general stimulate acid secretion. Orange juice and pop are acidic (160). Chocolate may relax the lower esophageal sphincter, accentuate gastroesophageal reflux, and result in dyspepsia which is not so much due to the ulcer, but to acid regurgitation in the esophagus.

2. Beverages

a) Milk

Milk is a poor neutralizer of gastric acid (58,136,241,412). Indeed, milk may stimulate acid secretion (241), possibly due to gastrin release or to direct stimulation of parietal cells by the protein and calcium in milk. Removal of calcium from milk prevents the increase in acid secretion in normal subjects but not in patients with a duodenal ulcer. The ingestion of large amounts of milk may be associated with the now-rare milk-alkali syndrome (356), and with atherosclerosis (468).

Milk has never been shown in a clinical trial, to be effective for the healing of ulcers, or for the relief of symptoms. Yet generations of patients have given testimony to their observation that milk helps their dyspepsia. Do our physiological observations create a heresy? Not necessarily so. Our patient's observations should humble us in the art of medicine, in the realization that milk may offer some benefit when taken in moderation and in conjunction with other therapeutic approaches, in the relief of pain. Indeed, in some studies, a $100 course of anti-ulcer therapy does no better than placebo in the relief of the patient's symptoms. "Regardless of whether its effect is symbolic, sacramental, or possibly physiologic, it [milk] does the job" (503).

b) Coffee, tea, juices and alcohol

Coffee, tea and caffeine may increase acid secretion (536), and both regular and decaffeinated coffee stimulate acid secretion (105). Epidemiological data have shown that coffee consumption is probably not associated with the development of peptic ulcer disease (168). Tea is a potent stimulant of gastric acid secretion (144). Among the constituents of the brewing of tea that might stimulate acid secretion are caffeine and theophylline. The evidence that fruit juices result in excessive acid secretion is inconclusive, (463,467).

Recent studies have shown that the direct effect of ethanol on the gastric mucosa under acute conditions is inhibition, not stimulation (111). There is no data on the effect of chronic ethanol ingestion on acid secretion in man, but in the rat chronic ethanol intake results in higher acid outputs following acute exposure to intravenous or intragastric ethanol, or in vitro exposure to mucosal ethanol as compared to studies using matched control rats (279). Serum gastrin levels were not significantly affected by ethanol. Furthermore, there is no evidence that the use of alcohol is associated with an increased frequency of duodenal or gastric ulcer except possibly in patients with cirrhosis (410). However, during the acute exacerbation of an ulcer, some patients will complain of coffee- or alcohol-related worsening of their pain. Under this circumstance, these beverages should be temporarily avoided. It is debatable whether intermittent and moderate use of ethanol alters gastric acid secretion, and no open-and-shut case can be made for prohibiting the occasional drink. It goes without saying that the best advice must always include the counsel to avoid overdrinking. Coffee, for some, like alcohol for others, is a vehicle for social interaction and relaxation, and there is no need to recommend total abstinence from coffee. Rather, moderation, like the middle of the road, continues to be the best place to travel.

3. Smoking

Cigarette smoking is associated with an increased incidence of duodenal ulcer and with decreased healing rates (134,168,210,251, 259,372,402,408,409,547,554). A British study found similar healing rates of duodenal ulcers in smokers and nonsmokers who were treated with cimetidine (2), while in an Australian study (277) 95% of nonsmokers healed their DU on cimetidine, ranitidine or oxmetidine, compared with only 63% of smokers. This difference was statistically significant. There was also a positive correlation between the failure to heal the patient's ulcer, and the number of cigarettes smoked. Furthermore, during a 12-month follow-up examination after healing and on no treatment, 53% of nonsmokers and 84% of smokers relapsed. Again these differences were highly significant. A second recent study also suggested that smoking increases the likelihood of relapse in duodenal ulcer after successful healing (496).

The mechanism of this effect is unclear (168). Nicotine has only a minor effect on acid secretion (547,554), but nicotine does depress the pancreatic output of bicarbonate (88). There is no evidence that smoking is a factor in the pathogenesis of GU, and the evidence that smoking affects the healing rate of GU is controversial (134,218). However, considering all the many major adverse effects of cigarette smoking on the patient's general health, and the possible or probable adverse effects of smoking on ulcer occurrence, healing and recurrence, it is prudent to advise patients to stop smoking.

4. Activity: Rest and Sedation

Two older studies suggested that hospitalization is associated with an increased healing rate of GU (137,218). However, the high cost of hospitalization has almost ended the practice of bringing patients with uncomplicated duodenal ulcers into the hospital for bed rest. Yet, the exception of course proves the rule, and some patients require this step - almost as a last resort before gastric surgery - to remove them from those so-important yet so poorly defined factors which result in the imbalance between aggressive and defensive factors, and precipitate the development of the ulcer. In the total approach to the patient, one needs to remind the individual that moderate amounts of activity are helpful adjuncts to a healthy life-style. This need for a balanced lifestyle is good advice, quite apart from any - as yet unproven - effect of activity on acid secretion, or ulcer healing and recurrence.

Sedatives

"A patient may be proud or ashamed of his duodenal ulcer" (503). While PUD is not caused by stress, feelings of anger or frustration may lower the patient's threshold for pain and raise the possibility of an ulcer recurrence. Perhaps more important than the use of sedatives is the use of time-honoured psychotherapy of the benefit of an understanding, supportive and encouraging role of the patient-physician relationship. Thus, sedatives, tranquilizers, or mood-altering drugs should not be given unless there is some reason other than the ulcer for their use in a given patient.

5. Drugs

Numerous observations all testify to the potential harmful nature of aspirin and ASA-like compounds in patients with gastric ulcers, as well as a generalized injurious effect of nonsteroidal anti-inflammatory agents on the upper gastrointestinal tract of persons who do not give a history of a previous ulcer diathesis (294,406). At least one third of ulcer patients develop dyspepsia following the ingestion of aspirin, aspirin-containing products, and other non-steroidal anti-inflammatory agents. The chronic ingestion of aspirin possibly leads to the formation of a gastric ulcer in a small number of chronic users (89,94,142). Chronic ulcer symptoms and/or disease may be more common in patients with rheumatoid disease, but it is unclear whether this is related to the underlying collagen-vascular disease. No similar association has been shown for duodenal ulcer or for duodenal bleeding. However, lack of proof does not prove that an association may not exist. It is unclear whether ASA actually causes ulcers de novo or causes ulcer recurrence in a person with ulcer diathesis. It is also unclear whether the commonly recognized ASA-related bleeding (358,521) is more often from the development of erosive gastritis, or the initation of bleeding from a pre-existing ulcer. It is also unclear whether adaptive cytoprotection occurs in a person chronically consuming ASA. Large total doses of adrenal corticosteroids may not necessarily lead to an increased incidence of gastric or duodenal ulcers (110). There is no evidence for or against the idea that use of the usual doses of antacids, H_2 blockers or sucralfate will reduce the risk of an ulcer developing in the patient who requires steroids or NSAIA's. Therefore, restriction of aspirin, NSAIA and steroid intake is prudent in the patient with known ulcer disease.

DRUGS USED FOR THE TREATMENT OF ACID-PEPSIN DISORDERS

Some double-blind endoscopically controlled clinical trials have established that numerous pharmacological agents are better than placebo in accelerating ulcer healing. The classification of these medications is based upon their site of action on acid secretion. In North America, the medications which are available for the treatment of acid-pepsin disorders include the H_2-receptor antagonists (cimetidine, ranitidine), anticholinergics, sucralfate, and antacids. Other effective agents are available in other parts of the world, and include the anti-gastrin proglumide, the antidepressant trimipramine, as well as carbenoxolone and TDB. Synthetic prostaglandins such as misoprostol and enprostil may be available in the near future for the effective and safe treatment of acid-pepsin disorders.

Table 7

CLASSIFICATION OF THERAPEUTIC AGENTS USED IN THE TREATMENT OF ACID-PEPSIN DISORDERS

NEUTRALIZATION		Antacids
"CYTOPROTECTION"		Prostaglandins Sucralfate Carbenoxolone TDB
H^+/K^+ ATPase		Omeprazole
CYCLIC AMP		Prostaglandins
CALCIUM CHANNEL BLOCKERS		Verapamil
RECEPTORS	H_2	Cimetidine Ranitidine Conventional Anticholinergic Drugs Antimuscarinic-Pirenzepine
	Gastrin	Proglumide
CNS		Sedatives Antidepressants

H_2-Receptor Antagonists

a) Cimetidine

With the thought and act of eating, both acid and gastrin are released. The volume of acid rises, and the pH of the gastric contents also rises, by about 2 units (328-332). The serum gastrin concentration initially rises, then falls. The serum gastrin concentration may be reduced by antral acidification, but the association is not a close one. The buffering effect of food is important, both in terms of neutralizing acid and in terms of buffering or breaking continued gastrin release.

Cimetidine is a competitive antagonist of histamine's action at the H_2 receptors. It inhibits gastric acid output, volume and pH in response to all known stimulants of acid secretion (190). The H_2

blocker cimetidine retains the imidazole ring of histamine, but has a modified cyanoguanidine side chain. However, the ring structure is not obligatory for H_2 blockage, since ranitidine, a highly potent H_2 blocker, has a furan ring. The action of cimetidine may be prolonged if it is taken with food (435), but there is no close correlation between blood levels of cimetidine and the pH of the gastric contents (331) Cimetidine reduces the output of basal and stimulated acid and pepsin secretion in normal healthy subjects, as well as in gastric and duodenal ulcer patients (332). The absorption of cimetidine from the gastrointestinal tract is good, with peak plasma concentration occurring approximately 90 minutes after oral administration (431). The half-life of cimetidine in blood is about two hours. Systemic bioavailability is approximately 70% with cimetdine and 50% with ranitidine. Both drugs demonstrate biexponential elimination curves from the plasma after intravenous administration and a bimodal curve after oral administration, which is probably the result of enterohepatic circulation. This bimodal peak may not be seen after four- or two-times a day dosing (331). The elimination half-lives of cimetidine and ranitidine are 1.7-2.1 hours and 2.1-3.1 hours, respectively, with apparent volumes of distribution approximately 50 L and 75 L respectively. Both drugs are eliminated, largely unchanged, via the kidneys.

The half-life of cimetidine is reduced in patients with severe liver disease (545), and in patients with renal insufficiency, the half-life of cimetidine in blood is prolonged. It has been suggested that the dose of cimetidine be decreased in these patients, and that dialysis patients should receive their dose of cimetidine after rather than before their hemodialysis. However, the effect of varying doses of cimetidine on gastric acidity in patients with renal insufficiency has not yet been reported, so that this suggestion of the need to adjust the plasma concentration of cimetidine must be made with caution. This is of particular interest since the plasma gastrin levels are high in patients with renal failure, since any excess cimetidine is removed by dialysis and since there is a poor correlation between plasma levels of cimetidine and the pH of the gastric contents in patients with duodenal ulcers without renal insufficiency.

Cimetidine and metiamide markedly reduce basal and nocturnal acid secretion (216,230,324,334,367), yet less than 30% of the overnight pH values will be greater than 3.5 (331). Cimetidine inhibits acid secretion in response to all known gastric stimulants, but most importantly, cimetidine reduces the gastric secretory response to food (216,331,434,435). With cimetidine 0.8-1.6g/day bid taken by mouth by patients with DU, about 20% and 40% respectively of the pH values are equal to or greater than 3.5 (331).

Cimetidine partially restores gastric secretion, where elevated, towards normal. That is, in the DU patient who is a "hypersecretor" in response to pentagastrin, histamine, or to food, the amount of acid secreted per unit time (mmol/hr) is returned towards normal levels. In contrast, most DU patients have the same concentrations of acid in their stomach - around the clock, after meals and during sleep - as do patients with gastric ulcers, gastroesophageal reflux disease, and indeed as do healthy volunteers. In these non-hypersecretors, the concentrations of acid are reduced following H_2 blockers to normal levels. This opens for discussion the second dilemma: how much acid inhibition is necessary for the relief of pain, and for ulcer healing? Until this question is satisfactorily resolved, there is little major implication which can be drawn from comparisons of the relative acid inhibitory effect of these various receptor antagonists. For example, relatively weak anti-secretory prostaglandins accelerate ulcer healing at rates comparable with the most potent anti-secretory agents (73).

After chronic cimetidine therapy, gastric acid secretion is not enhanced. That is, there is no evidence of acid rebound following a course of cimetidine. Animal studies have shown that there is no change in the parietal cell mass after 12 months of cimetidine treatment (304). Indeed, in duodenal ulcer patients, both the mean peak acid output and the mean maximal acid output were 25% lower after three months of therapy with 1.6 g cimetidine daily (497,498). This suggests that there may even be a decrease in the parietal cell mass after prolonged use of cimetidine (79).

The fasting serum gastrin concentration is probably unaffected by cimetidine, but the food-stimulated gastrin-response is greater than in patients not taking cimetidine (323,331,420,432,434,435). This high gastrin-response in patients taking cimetidine is related only in part to the reduced acid-inhibition of gastric secretion. In patients with DU, cimetidine does not affect the rate of gastric emptying or of pancreatic enzyme output after meals (323,434,435).

The clinical significance of these acute changes in post-prandial gastrin concentration are obscure. The effect of cimetidine to increase serum gastrin levels may be partially due to the elevation of intragastric pH (432,434,435). When the degree of acid inhibition was comparable in response to food in patients given cimetidine or a synthetic prostaglandin (330), or in response to histamine-stimulated acid secretion in rats given cimetidine or YM-11170, a new chemically distinct H_2-receptor antagonist (397), the serum gastrin responses to food were significantly greater with cimetidine. This suggests that the increase in serum gastrin levels by cimetidine is not due just to the chemical nature of the antisecretory agent or to the elevation of intragastric pH, but is probably due in part to a direct effect of cimetidine on the release of gastrin. Of importance, basal and stimulated gastrin levels did not change after three months' treatment with cimetidine (497,498).

Cimetidine is no better than placebo in the relief of pain in patients with GU (534), and is equivalent to antacid in the immediate relief of pain. In patients with DU, cimetidine is equivalent to or possibly better than placebo to relieve daytime and nighttime pain (54,64,188,190,223).

Cimetidine, 1.0-1.2 g/day for 4-6 weeks, is useful to heal GU (167,169,244,479,534). Similarly, cimetidine 0.8-1.6 g/day for 4-6 weeks, is effective in the endoscopically-proven healing of DU (27,29,32,54,60,64,188,189,190,220,223,478). In the United States, cimetidine is significantly more effective than placebo in the healing of duodenal ulcers at two weeks, and at all time periods in Europe (190,194). The striking disparity is between the American and the European placebo-healing rates. Bardhan (26-32) has reviewed 20 double-blind placebo-controlled studies of duodenal ulcer healing, and has found that cimetidine significantly increased the percentage of duodenal ulcers healed (75%) compared to placebo treatment (38%) in 4 to 12 weeks. In the one reported blinded trial of cimetidine in the treatment of gastric ulcer, 69% of patients taking cimetidine healed in 4 weeks, whereas in the placebo group, 37% healed within the same time period.

It must be stressed that widely different rates of ulcer healing have been reported: after a four week course of cimetidine, healing rates range from 59% to 85% for DU (54,60,64,151,188,189,220,242,476), and from 69% to 83% for GU (4,16,98,129,148, 167,169,233,244,479). The literature includes numerous possible explanations for the different healing rates: variations in dose, or therapeutic regimen, concomitant use of antacids, poor patient compliance, hypersecretory states, pyloric stenosis, interaction with other drugs, smoking, alcohol, and ideopathic, i.e. "slow healers" (30,60,64,187-189,220,223,496). Also, the placebo-healing rate varies widely, and the explanation for this phenomenon remains unclear.

Cimetidine 600 mg bid is as effective as 300 mg qid in accelerating duodenal ulcer healing and relieving pain (393). Cimetidine given as a single nocturnal dose of 800 mg is at least as effective as cimetidine, 400 mg bid, in prompting the healing and alleviating duodenal ulcer symptoms (124). Also, cimetidine, 300-400 mg at nighttime, is effective in preventing ulcer recurrence (396). No increase in ulcer recurrence rate was noted in patients who initially healed with cimetidine or placebo. Indeed, cimetidine may reduce the frequency of relapse after DU healing (31).

While cimetidine is clearly indicated for the treatment of DU and GU, as well as gastroesophageal reflux disease, there is widespread and occasionally indiscriminate use of cimetidine (471). However, many patients with chronic ulcer disease will have frequent recurrences of symptoms, and it may be argued that the use of H_2-blockers may be appropriate in this setting, without performing frequently repeated endoscopies.

b) Ranitidine

Ranitidine has a furan ring in place of the imidazole ring of cimetidine. Ranitidine is at least twice as effective as cimetidine against basal- and gastrin-stimulated acid secretion, on a weight-for-weight basis. Twenty-four hour intragastric acidity and nocturnal acid output were measured in 12 patients with chronic duodenal ulcer disease (184). Ranitidine 150 mg bid or 300 mg nocte, was significantly more effective at decreasing intragastric acidity and nocturnal acid output than cimetidine 400 mg bid or 300 mg nocte. There was no difference between twice daily ranitidine and nighttime ranitidine, or between twice daily cimetidine and nighttime cimetidine, in the reduction of intragastric acidity.

In the United States, a large multicentre trial demonstrated the superiority of ranitidine plus antacid over placebo plus antacid in the healing of duodenal ulcers after 2 or 4 weeks of treatment (224). Numerous other international studies have also confirmed the accelerated rate of healing of gastric and duodenal ulcers. With ranitidine, the 4-week healing rate for GU varies from 63-86%, and from 71-90% for DU (71).

A European multicenter study comparing ranitidine and cimetidine in 292 patients with gastric ulcer revealed similar healing rates at 4- (69% and 59%, respectively) and 8-weeks (90% and 88%, respectively) (36). Approximately similar 4- and 8-week healing rates for gastric ulcer using ranitidine and cimetidine were reported in an Australian study including 44 outpatients with endoscopically proven lesions

(264).

A recent study performed on 109 patients with endoscopically proven DU were prospectively randomized double-blind to receive ranitidine 150 mg bid or 300 mg before bedtime. After four weeks on ranitidine, 84% healed on the bid regimen, and 95% healed on 300 mg nocte (106). Thus, ranitidine 300 mg administered as a single nighttime dose for the treatment of duodenal ulceration, is at least as good as, and probably better than the conventional 150 mg bid. An Italian multicentre study has confirmed the benefit of this simplified once-a-day dosage regimen (130).

Not all ulcers heal with cimetidine, and patients are now appearing who are resistant to healing and to suppression of acid secretion (268). There have been three reports of ranitidine healing cimetidine resistant ulcers after 4-8 weeks of therapy (82,370), with healing rates varying from 50-83%. Thus, ranitidine, 150 mg twice daily, increases the rate of healing of duodenal and gastric ulcers in about 90% of patients treated for up to two months. Ulcers resistant to ranitidine treatment are uncommon and ranitidine heals ulcers resistant to other drugs, e.g. cimetidine (71).

The decision to use ranitidine or cimetidine remains controversial (310,352). Major differences between these agents are found in cimetidine's biological activity at sites other than the gastric H_2-receptors, resulting in adverse events, the greater convenience of the once or twice a day dosing with ranitidine, and the lower rate of breakthrough ulceration in patients on ranitidine versus cimetidine maintenance (Table 8).

Table 8

POTENTIAL ADVANTAGES OF RANITIDINE VERSUS CIMETIDINE

1. ADVERSE EVENT PROFILE, ESPECIALLY LACK OF DRUG INTERACTION
2. CONVENIENCE OF ONCE- OR TWICE-A-DAY THERAPEUTIC REGIMEN
3. LOWER RATE OF BREAKTHROUGH ULCERATION WHILE ON MAINTENANCE THERAPY

In summary, the H_2 receptor antagonists represent the gold standard for the treatment of peptic ulcer disease. Ranitidine has several potential advantages over cimetidine which may prove to be sufficient reason for ranitidine to be the H_2 blocker of choice.

Adverse Event Profile of H_2 Receptor Antagonists

About 30% of patients taking placebo for the treatment of peptic ulcer disease will have minor side effects, and the same minor and insignificant side effects may occur with the H_2 blockers. Worldwide, pre- and post-marketing surveillance has shown cimetidine to be a safe medication (354), a point which must be stressed when considering the totally disproportionate degree of interest shown in the rare side effects. These side effects are summarized in Table 9.

Table 9

SIDE EFFECTS OF CIMETIDINE (McGuigan, 1981)

1. CNS	mental confusion, somnolence, lethargy, restlessness, disorientation, agitation, hallucinations, twitching, seizures, flushing, unresponsiveness and apnea; more common in young and old, and in patients with impaired hepatic and renal function
2. CV	bradycardia
3. Hematological	neutropenia immune response
4. Endocrine	antiandrogen effects: gynecomastia, loss of libido, impotence, reduction in sperm count hyperprolactinemia: galactorrhea
5. Liver	mild and reversible elevations in serum transaminase levels adverse drug-drug interactions
6. Kidney	-mild elevations in serum creatinine

Indeed, cimetidine has an enviable record of clinical safety, despite the litany of potential and actual side effects. In a small number of cases, cimetidine has been found to cause granulocytopenia, gynecomastia, transient male sterility, mental confusion, and adverse drug-drug interactions (354).

Cimetidine crosses the blood-brain barrier, and this is presumably the basis for the mental confusion, sleepiness, or mood changes which have been reported, particularly in older people with impaired renal function (473). This adverse event is very much less common with ranitidine than with cimetidine. Cimetidine is known to modulate the immune response by decreasing T-lymphocyte function via blockage of H_2 receptors (12,442). The rise in serum creatinine is of questionable clinical significance except in the patient with renal failure. Ranitidine does not affect the WBC and does not alter renal function.

Of importance, cimetidine, but not ranitidine, interacts with the hepatic microsomal enzyme systems, thereby reducing the activity of these systems and altering the clearance and enhancing the toxicity of many drugs such as theophylline, warfarin, propranolol and diazepam (127,248,269,426). The degree to which cimetidine decreases drug clearance is dependent upon the fraction of drug eliminated by the inhibited metabolic rates, the route of administration for high hepatic extraction drugs, and individual patient characteristics (422). Ranitidine has a very low binding affinity for cytochrome P-450, and at therapeutic doses does not decrease the clearance of those drugs which are affected by adverse (drug-drug) interactions with cimetidine. Therefore, the dose of numerous medications such as anticoagulants, bronchodilators, hypnotics, antihypertensives and anticonvulsants need to be lowered in patients taking cimetidine in order to prevent toxic side effects from these medications. The dose of cimetidine cannot reasonably be reduced to prevent these interactions, since the ulcer for which the H_2 blocker was prescribed may then fail to heal. Indeed, when patients are on cimetidine plus a second or third interacting medication, it must be stressed to the patient that it would be unwise for them to abruptly change the dose or to stop taking their cimetidine.

Cimetidine and ranitidine decrease indocyanine green clearance, but this does not necessarily indicate a significant effect on liver blood flow. Hypersensitivity hepatitis has been reported in one patient exposed to cimetidine on several occasions (545).

Recent studies have reported that 8% of men with gastric hypersecretory disorders treated with high doses of cimetidine develop impotence, gynecomastia, and breast tenderness (252,351). Gynecomastia and transient sterility are attributed to the fact that cimetidine is antiandrogenic and competitively inhibits testosterone binding to receptor sites. As a result, less than 1% of men chronically taking high doses of cimetidine may develop painful enlargement of the breast. Gynecomastia has been reported however after lower doses used for shorter periods, but the condition quickly disappears when the cimetidine is discontinued or when ranitidine is substituted. Cimetidine, but not ranitidine, inhibits penile erection in rats. In males with gastrinoma maintained on high doses of cimetidine, impotence has been reported. Cimetidine produces a rapid rise in plasma prolactin in both normal and amenorrheic women (91,347). Intravenous but not oral cimetidine raises the serum prolactin levels.

While peptic ulcer disease is rare during pregnancy, pregnant women frequently experience gastrointestinal symptoms, due at least in part to the reflux of gastric acid into the esophagus, and to gastric atony. The use of cimetidine is not recommended during pregnancy. A recent study has focused on the adverse early and late effects of cimetidine but not ranitidine on sexual function of male rat pups whose mothers were given H_2 blockers during pregnancy: reduced anogenital distance, weight of testes and ventral prostate-seminal vesicles, reduced testosterone levels, and diminished sexual behavior (403). While these results cannot be directly applied to man, the work does raise the concern that the use of cimetidine by pregnant women might result in unwanted feminization and adverse long-term sexual behavior in the male offspring of such women.

Other Potential Side Effects of H_2 Receptor Antagonists

1. Absorption

Absorption across a membrane is generally favored when a drug is in its un-ionized form. Increased conjugation could result in decreased drug absorption. Increased gastric pH resulting from H_2-antagonist administration may also prevent the degradation of acid labile compounds. The bioavailability of the antifungal Ketoconazole is reduced when administered two hours following cimetidine. It is disputed whether cimetidine interferes with the absorption of tetracycline but it is generally agreed that the absorption of protein-bound cobalamine but not the crystalline vitamin B_{12} is reduced by therapeutic doses of cimetidine. The only study in which the effects of ranitidine on drug absorption have been evaluated demonstrated an enhancement of the absorption of the water-soluble benzodiazepine, midazolam.

2. Nitrosation

Nitrosation of cimetidine may occur in the stomach, and the intermittent reduction in the intragastric acidity occurring in patients taking cimetidine has raised the issue of whether long-term therapy with H_2 blockers may predispose to the development of gastric cancer. Many foods, drugs and beverages undergo nitrosation, many amines are nitrosated, and the resulting nitrosamines may be carcinogenic (366,381,429,455). There is no final answer to this theoretical concern, but most authorities would agree with the judicious long-term use of H_2-receptor antagonists in carefully selected patients with peptic ulcer disease.

SUCRALFATE

Sucralfate is a basic aluminum salt of sucrose octasulfate. Sucralfate is a potent anti-ulcer drug (342,345,349) and is effective in reducing the recurrence rate of gastric and duodenal ulcers . On encountering gastric acid, sucralfate becomes a highly condensed, viscous substance with the capacity to buffer acid (383,384,523). Sucralfate forms complexes with proteins and prevents their hydrolysis, by preventing pepsin-substrate interaction. Sucralfate also inhibits peptic activities by direct adsorption of pepsin. Finally, sucralfate adsorbs bile salts. Neither food nor antacid alters the selective binding of sucralfate to ulcer sites (182). Sucralfate has a protective effect on the gastric mucosa of rats exposed to ethanol or taurocholic acid (209).

Sucralfate is superior to placebo and equivalent to cimetidine in the symptomatic improvement and healing of gastric and duodenal ulcers in patients studied in the United States, Taiwan, Austria, Canada, Finland, Holland and Belgium (217,228,283,345,414,513). For example, in controlled studies conducted outside the United States, in 299 patients, sucralfate was found to be statistically superior to placebo and equivalent to cimetidine in ulcer healing (342,344,355). Hollander et al, in a recent U.S. multi-center study utilizing endoscopy, found sucralfate to be superior to placebo in a study of 55 patients after 4 weeks treatment (228). McHardy (355) reported on 216 outpatients with duodenal ulcers: sucralfate was superior to placebo in ulcer healing and reduction in both diurnal and nocturnal ulcer pain. In a review of the world literature of ten years clinical experience with sucralfate (158,245), only constipation and mouth dryness were slightly more frequent than in control subjects.

The recurrence of duodenal ulcer over a one year period was twice as great when patients were taking placebo as compared with sucralfate (378). Patients whose duodenal or gastric ulcers had healed on cimetidine relapsed earlier than did those whose ulcers had healed on sucralfate, but the cumulative relapse rate by the end of one year was about 70% in both groups (339). The mean duration of remission in patients who developed a recurrence was significantly greater in patients treated initially with sucralfate than in those treated initially with cimetidine - 7.3 and 4.6 months, respectively. Furthermore, when patients with healed duodenal ulcers were maintained on placebo, those who had been initially treated with H_2-receptor blockers for acute ulcer had significantly more relapses than patients who had been treated with other drugs. This raises the exciting possibility that sucralfate may alter the natural history of peptic ulcer disease, at least in the short term. The remission rate at 6 months (102,309), or at 6 and 12 months (378) in a large number of patients with duodenal ulcer maintained on sucralfate, was superior to that achieved by placebo.

No difference in relapse rate was found in 55 gastric ulcer patients maintained for 6 months on sucralfate or placebo (102).

In summary, sucralfate is highly effective for the treatment of peptic ulcer disease and represents one of the first-line therapeutic drugs of choice.

ANTICHOLINERGICS

A muscarinic action occurs at the neuro-effector junctions of all postganglionic cholinergic fibers. A nicotinic action occurs at the ganglionic synpases and the neuromuscular junctions. Atropine has no effect on 24-hour intragastric acidity or nocturnal acid output when given alone or in combination with cimetidine (418) or ranitidine (108). In contrast, propantheline bromide, isoproamide and pirenzepine each reduce acid secretion when given with cimetidine to a greater extent than when the latter is given alone (25,329). Thus some synthetic anticholinergics may be more effective than natural belladonna alkaloids, in near-maximal tolerated doses, in reducing acid secretion, or enhancing the effect of H_2-blockers.

Anticholinergic drugs are used to inhibit competitively the effects of acetylcholine released from postganglionic parasympathetic nerves. Interdigestive and food-stimulated acid output is depressed (53) by about one third, using doses of anticholinergics just below the tolerance level. For most anticholinergic drugs, a sufficient dose of these tertiary or quarternary compounds which reduces gastric secretion will also induce pupillary dilatation, bladder obstruction, a dry mouth, and glaucoma in the susceptible person not taking miotics.

Oral administration of anticholinergics at the optimal therapeutic dose reduces basal acid secretion by 50% (33,141), reduces the histamine-or gastrin-stimulated acid secretion rate by about 40% (141), and reduces the food-stimulated secretion rate by about 30% (53,108,368). There is only limited evidence supporting the use of anticholinergics in the relief of symptoms, healing or prevention of ulcer disease (14,247). Adding bedtime anticholinergic to an antacid regimen is not associated with significant improvement of duodenal ulcer healing rate (73). Glaucoma, obstructive or neurologic uropathy, gastric retention and severe inflammatory bowel disease are contraindications to the use of anticholinergic drugs.

Pirenzepine is a newly developed anticholinergic drug which differentiates between the muscarinic receptors in various organs, binding with a high affinity to the muscarinic parietal cells, while only binding weakly with the receptors of other exocrine glands or smooth muscles (56,205,404). Pirenzepine inhibits basal and pentagastrin-stimulated acid secretion in man (79,84,147). It has no effect on intragastric pH but does potentiate the effect of cimetidine on intragastric H^+ activity (329). With correction for pyloric loss and duodenal reflux, pirenzepine was associated with a reduction in basal, maximum and peak acid output, basal and maximum acidity, and basal and maximum volume (424). Cimetidine 400 mg showed about twice the inhibitory activity of pirenzepine 50 mg on basal and stimulated secretion. In another recent study, pirenzepine was shown to have no significant effect by itself on acid output or concentration overnight or in response to food, but did enhance the effect of cimetidine (329). Londong et al (321,322) also studied the combination of cimetidine and pirenzepine, given intravenously and in a ratio of 10:1: almost complete acid inhibition was obtained but some patients developed unpleasant and unwanted muscarine side effects.

In a single-blind controlled Austrian multi-center study involving 126 patients with duodenal ulcer, the efficacy of pirenzepine 50 mg bid in ulcer healing and pain relief was comparable to cimetdine, 1 g/day (83,84). This confirms the results of other controlled studies (23,50,115). A recent review of double-blind, therapeutic studies has revealed healing rates of ulcer at pirenzepine doses of 100-150 mg/day of between 54-84% in trials with 718 duodenal ulcer patients and 630 patients with gastric ulcer (526). The incidence of the expected parasympatholyte adverse events was low. Thus, pirenzepine, given by itself, accelerates the healing of duodenal and gastric ulcers. It needs to be established whether pirenzepine should be used as a first choice medication in the treatment of ulcer disease, or whether it should be used in combination with H_2-blockers.

ANTACIDS

Antacids are chemicals that neutralize the hydrochloric acid secreted by the gastric parietal cells. Numerous studies have shown accelerated ulcer healing in patients who ingest enough antacid to neutralize gastric contents (229,317,408). Although antacids are recognized as being useful for ulcer healing, their efficacy in relieving the pain of ulcer disease has been questioned (510,512). This holds both for the relief of an episode of pain and for the reduction in the number of symptomatic days by a course of antacid or placebo. The major goals of antacid therapy are to reduce the acidity of gastric contents, to reduce the load of acid delivered into the duodenum, and to diminish peptic activity by increasing the luminal pH above that acidity which is optimal for proteolysis. Pepsin is inactivated at pH's above 2.3-4.0, depending on the substrate used to measure the peptic activity (185). With the reduction in acidity and peptic acitivity, antacids should accelerate ulcer healing, and hopefully improve symptoms of pain.

Chemical Basis of Antacid Action

1. Sodium Bicarbonate

Sodium bicarbonate is water soluble and rapidly undergoes this reaction in the stomach:

$$NaHCO_3 + HCL \rightarrow NaCL + H_2O + CO_2$$

Because sodium bicarbonate can produce alkalosis, promotes fluid retention because of its sodium content, and because it is rapidly emptied from the stomach owing to its solubility, sodium bicarbonate is not recommended for long-term use as an antacid.

2. Aluminum Hydroxide.

Aluminum hydroxide is relatively insoluble in water, but the slow approach to equilibrium to form chloride salts and the formation of complex hydrated ions makes the situation complex (336). Aluminum hydroxide reacts with hydrochloric acid in the stomach to form poorly-absorbed aluminum chloride. When present in adequate amounts, it raises gastric pH to 4 to 4.5, neutralizing approximately 30 mEq of hydrogen ion per gram of aluminum hydroxide. It may inhibit gastric smooth muscle contractions (212,213) sufficiently to delay gastric emptying; this effect of aluminum-containing antacids on smooth muscle is thought to take place as a result of the aluminum interfering with calcium fluxes and excitation-contraction coupling in intestinal smooth muscle (213).

Aluminum is poorly absorbed by the small bowel but detectable plasma aluminum concentrations after aluminum-containing antacids have been reported (258). Circulating aluminum is cleared by the normal kidney; increased deposition in tissues has been observed (428).

Aluminum hydroxide binds bile acids (318), which may contribute to its antidiarrheal properties.

Drying of the aluminum hydroxide gel causes it to become nonreactive and ineffective as an antacid. Depending upon the manufacturer's process, there are great differences in the solubility of different preparations in acid solution and thus there may be wide variations in the rate of neutralization of gastric acid (76). The solubility of aluminum decreases as the pH is raised. Small amounts of aluminum are likely absorbed from the intestine (258). Aluminum absorption may be parathormone-dependent (335) which may account for the aluminum retention that has been shown to occur in some patients with chronic renal disease who take aluminum hydroxide to treat hyperphosphatemia (5,44). Under these circumstances, aluminum toxicity has been claimed, and phosphorous depletion may occur (76,101).

Aluminum hydroxide gel (Amphojel) contains 640 mg $Al(OH)_3$ per 10 ml, which will neutralize 19.3 mEq H^+, i.e. 5.2 ml $Al(OH)_3$ is needed to neutralize 10 mEq of H^+. Each 10 ml contains approximately 13.8 mg of sodium.

3. Calcium Carbonate. Calcium carbonate reacts with hydrochloric acid in the stomach to form calcium chloride. When present in excess, it raises gastric pH to 7.5, while neutralizing approximately 13 to 17.5 mEq of hydrogen ion per gram of calcium carbonate. Each 10 ml of Camalox® contains 500 mg $CaCO_3$, 450 mg $Al(OH)_3$, and 400 mg MgO. This will neutralize 35.9 mEq of H^+; 2.8 ml is required to neutralize 10 mEq of H^+. Despite its potency, calcium carbonate may produce a number of systemic complications, presumably due to the absorption of some $CaCl_2$, especially as gastric acidity is increased (246) This leads to hypercalcemia, the milk alkali syndrome, and acid rebound. Acid rebound in the stomach has been shown to occur after the neutralizing capacity of the calcium carbonate has been exhausted (38,161). Acid secretory rebound, which may be mediated by gastrin release, probably is due to the local action of calcium on the parietal cells (231) in addition to systemic hypercalcemia (42). Although rebound occurs more frequently after higher doses of calcium carbonate (4 g), oral doses as small as 0.5 g may enhance acid secretion in normal subjects (306).

4. Magnesium Hydroxide. Magnesium hydroxide is poorly soluble in water, and reacts rapidly with hydrochloric acid in the stomach to form poorly-absorbed magnesium chloride:

$$Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$$

When in excess, it raises gastric pH to over 9, while neutralizing approximately 30 mEq of hydrogen ion per gram of magnesium hydroxide, or 2.7 ml of H^+ per ml of milk of magnesia. The insolubility of $Mg(OH)_2$ may slow its emptying from the stomach and may prolong its duration of action (211). Only a small amount of the magnesium salts is absorbed (211).

5. Combination Antacids. Differences among the various antacids relate to their neutralizing capacity (potency), their rapidity of action with gastric acid; their gastrointestinal side effects, and their systemic complications. Mixtures of aluminum-, calcium-, and magnesium-containing antacids frequently are dispensed in an attempt to avoid the undesirable properties of each component, especially their effects on colonic function. In contrast to aluminum hydroxide, which cannot raise gastric pH above 5, or magnesium hydroxide, which elevates pH to over 9, combinations of these components maintain pH at a maximum of 6.5 to 7.5 (145,162,163). Al-Mg antacids are preferred to $NaHCO_3$ because of the latter's high sodium content, short duration of action, and tendency to produce alkalosis. Calcium-containing antacids are out of favor because they stimulate acid secretion and may produce hypercalcemia and impaired renal function. Milk is not a satisfactory antacid. Indeed, it stimulates acid secretion (241) and when taken in excess it may lead to the milk-alkali syndrome and to atherosclerosis.

The sugar and sodium content of most antacids have been greatly minimized (436) such that neutralizing capacity, cost convenience, and palatability (446,474) are the major factors for selection of a liquid antacid product.

C. Clinical Antacid Pharmacology

1. Gastric Acidity

The degree to which each patient responds to antacid depends on the rate of emptying of the antacid from the stomach, as well as on the gastric secretory response to food. The acid secretory response to a meal, measured by in vivo titration to pH 5.0 in patients with duodenal ulcer, showed that acidity was near zero for two hours after the antacid was ingested, rising to only about 3 mEq/l by 3 hours after dosing (162). This compared with a gastric acidity of 70 mEq/l when patients took water with the meal.

2. Dose-Response Relationships

The dose of antacid needed to achieve acid neutralization may vary from patient to patient, depending upon their acid output in response to food. Based on in vitro studies, it has been suggested that patients whose maximum acid output is greater than 20 mEq/hr require 80-160 mEq of buffer, which is equivalent to 30 to 60 ml of magnesium hydroxide or magnesium/aluminum hydroxide mixtures (162). In normosecretor patients, 40-80 mEg, or 15-30 ml is considered to be an effective dose.

Patients whose peak histamine response was greater than 24 mEq per hour ("hypersecretors") required higher doses of antacid to reduce gastric acidity than did those patients with a peak histamine response of less than 17 mEg per hour ("hyposecretors").

3. Timing of Administration

Antacids ingested on an empty stomach are quickly evacuated and their acid-neutralizing effects are brief (192-194). When administered with meals, the action of antacids is more prolonged (162,163).

When an antacid mixture of aluminum and magnesium hydroxides, such as Maalox® or Mylanta®, is given to patients after a meal, it produces a sustained though fluctuating increase of intragastric pH (122). The time of administration should be carefully chosen, for it is necessary to take advantage of the elevation of intragastric pH produced by the diluting and buffering action of the meal itself. By the end of the first postprandial hour, the intragastric pH is rapidly declining and at that time ingestion of a dose of antacid will be utilized most effectively to reduce gastric acidity. By the end of the third postprandial hour the pH is declining again, since the first dose of antacid has already been partially consumed or emptied. At this time, a second dose of antacid raises the pH again for at least an hour. It would be expected that another meal and another cycle of antacid administration would follow at regular intervals, thus keeping the intragastric pH almost continuously elevated. The results of the recent study of Mahachai et al (328) are of interest in this regard, and demonstrate the efficacy of seven times a day antacid in lowering intragastric pH. This effect is particularly noteworthy during the daytime. Combining antacids with cimetidine may prove to be useful combination therapy, with an increase in the number of pH readings at or above 3.5.

Measuring the effect of antacids on duodenal acid load is particularly important since reduction of duodenal acid load is the major aim of antacid therapy in patients with duodenal ulcer disease. Furthermore, duodenal acid load depends on efficiency of neutralization, gastric secretion and gastric emptying. For about one hour after the ingestion of a meal, negligible amounts of H^+ ion enter the duodenum (122). This low duodenal H^+ load is due to buffering and dilution of acid by the protein in the meal. After the first hour, the effect of the meal is rapidly diminished, duodenal acid load rises sharply and remains high for several hours. However, two doses of Maalox® spaced one and three hours after the meal produced a marked reduction in H^+ duodenal load.

4. Relative Potency of Different Antacids

The effective potency of antacids needs to be established experimentally. The amount of 0.1 N HCl (100 mEq H^+/1, pH1) that can be added over a two-hour period to 1 ml of liquid antacids without reducing the pH below 3.0 (1 mEq H^+/1) correlates well with relative antacid potency *in vivo* in patients with gastric and duodenal ulcer (162-164). The composition (Table 10) and the potency (Table 11) of commonly-used antacids varies widely.

D. Complications of Antacid Therapy

There are many (Table 12) but fortunately relatively uncommon, complications associated with the chronic use of Al-Mg antacids (5,18,80,235-239,316,325,539,546).

TABLE 10. COMPOSITION OF COMMONLY USED ANTACIDS

Composition (mg per 10 ml)

Name	$Al(OH)_3$	$Mg(OH)_2$	$MgSi_3O_8$	Other	Sodium mg/10 ml
Amphojel	640				13.8
Gelusil	500		1000		16
Maalox	400	400			1.7
Mylanta	400	400		Simethicone 40 mg	23
Mylanta II	800	800		Simethicone 80 mg	8.2
Riopan				Magaldrate 800 mg	1.4

Composition and sodium content from Handbook of Non-Prescription Drugs. American Pharmaceutical Association, ed. 5, 2-17, 1977; or from Schneider and Roach (474).

TABLE 11. POTENCY OF COMMONLY USED ANTACIDS

Name	mEq H^+ neutralized per 10 ml	ml to neutralize 10 mEq H^+
Amphojel	19.3	5.2
Gelusil	13.3	7.5
Maalox	25.8	3.9
Mylanta	23.8	4.2
Mylanta II	41.4	2.4
Riopan	22.1	4.5

Potency data from Fordtran et al (163)

Table 12. COMPLICATIONS OF ANTACID THERAPY

SYMPTOM	CHEMICAL BASIS
Constipation	Al
Diarrhea	Mg
Phosphate depletion	Al
Hypermagnesemia	Mg
Neurological defects in chronic renal disease	Al
Sodium overload	Na
Interference with drug absorption	

a) Phosphorous Depletion

All aluminum-containing antacids, with the exception of aluminum phosphate, will form insoluble salts of phosphorous and will thereby reduce the rate of phosphorous absorption. In patients with normal renal function a phosphate depletion syndrome may rarely be observed. Phosphate depletion is characterized by decreased phosphate absorption, decreased urinary phosphorous, hypophosphatemia, and hypercalciuria due to skeletal resorption (499). Symptoms of phosphate depletion include anorexia, weakness, malaise and bone pain. If severe and prolonged, phosphate depletion and incresed skeletal resorption can lead to osteomalacia, osteoporosis, and fractures.

b) Cation Absorption

Many commercial antacids contain relatively large amounts of sodium and their use may be associated with fluid retention, particulary in patients with renal insufficiency.

Significant absorption of aluminum occurs in normal subjects ingesting aluminum hydroxide antacids (258,428). In renal failure, aluminum levels can be quite high in plasma, bone and muscle. Brains from these uremia patients dying of an encephalopathy syndrome also have a high aluminum concentration (5,539).

Five to ten percent of the magnesium in magnesium hydroxide can be absorbed, but hypermagnesemia occurs only very rarely in patients with renal insufficiency. Calcium can be absorbed when calcium carbonate combines with gastric acid to form soluble calcium chloride. Although pancreatic bicarbonate converts most of this back to the insoluble carbonate salt, about 10% remains as calcium chloride (101). If renal function is normal, chronic hypercalcemia probably does not occur if less than 20g a day of calcium carbonate is ingested (211). If renal function is depressed, hypercalcemia may develop with as little as 4 g per day.

c) Alkalosis

All antacids promote the development of a metabolic alkalosis, to some degree. Initiation of an alkalosis depends upon the irreversibility of the reaction of the antacid with gastric acid, but perpetuation of the alkalosis depends upon impaired renal function (211). For every equivalent of hydrochloric acid produced by the parietal cell, an equivalent of sodium bicarbonate is also produced. Acid is secreted into the gastric lumen, and bicarbonate is discharged into the bloodstream. If the HCl is re-absorbed in the duodenum or is neutralized by pancreatic juice, then acid-base balance is maintained.

If the HCl is neutralized by an antacid, it becomes unavailable for either re-absorption or reaction with pancreatic bicarbonate, and alkalosis will result. This is particularly prone to occur with sodium bicarbonate, since the NaCl produced in the reaction does not react with carbonate, phosphate, or hydroxide ions later in the gastrointestinal tract, so that no HCl is re-absorbed, and a base excess is produced.

d) Milk Alkali Syndrome

The milk alkali syndrome can occur whenever there is a high calcium intake combined with any factor producing alkalosis. Calcium can be provided by ingestion of large amounts of milk or large doses of calcium carbonate. Alkalosis may be produced by vomiting, or by any antacid taken in large volumes. The main features of the syndrome are hypercalcemia, elevated blood urea nitrogen and creatinine levels, and frequently the presence of alkalosis (356).

e) Acid Rebound

Food stimulates gastrin release and acid secretion. Normally hydrochloric acid will then suppress further gastrin release, and taking antacid will neutralize the acid and should theoretically lead to failure of gastrin suppression and more food-stimulated acid secretion. This may be a usual phenomenon of antacid in the stomach, but acid rebound is defined as sustained hypersecretion of gastric acid after antacid has been emptied from the stomach. Only calcium carbonate has this effect (42) likely through the mechanism of hypercalcemia and gastrin release. The degree of hypersecretion induced by a single dose of calcium carbonate after meals is minimal in most persons, but some individuals are quite sensitive and gastric secretory rates may be high in response to calcium-containing antacids

Antacid Drug Interaction

In Table 13 is summarized the many antacid drug interactions reported in humans. Tetracycline and cimetidine absorption may be impaired by antacids (508). Antacids may enhance the absorption of Coumadin, thereby increasing its potential side-effects. Some antacids may alkalinize the urine and will thereby alter the renal excretion of some drugs. For example, the more alkaline the urine, the more aspirin will be excreted and therefore the lower the blood levels (308).

The mechanisms of the effect of antacids on drug absorption include delayed gastric emptying, absorption of drug, binding of bile salts, and altered urinary pH and drug excretion (9,239).

TABLE 13. ANTACID DRUG INTERACTIONS REPORTED IN HUMANS

	Depressed Drug Level or Effect	Enhanced Drug Level of Effect
GI TRACT	Cimetidine[b]	
ANTIMICROBIALS	Isoniazid[a]	Solfonamides[b,c]
	Tetracycline[a,b,c]	
CARDIOVASCULAR SYSTEM	Digoxin[a,b]	Dicumarol[b]
	Propranolol[a]	Quinidine[a,b]
CENTRAL NERVOUS SYSTEM	Chlordiozepoxide[a,b]	Amphetamine[c]
	Chlorpromazine[a,b]	Levodopan[a,b]
	Phenytoin	
NON-STEROIDAL ANTI-INFLAMMATORY AGENTS	Aspirin[a,b]	Naproxen[c]
VITAMINS	Iron[c]	
	Phosphorus[a]	
	Vitamin A[a]	

a - aluminum hydroxide

b - magnesium hydroxide

c - $NaHCO_3$

Data summarized from Hurwitz (235-239).

Clinical use of Antacids

It is only recently that evidence has been obtained that antacids may promote peptic ulcer healing. In two early controlled trials (40,132), intensive antacid therapy did not benefit healing rate. This lack of effect in the controlled trial of Doll et al (132) may have been due to their use of an intragastric drip of 40 g sodium bicarbonate daily in hospitalized patients. Baume and Hunt used 4g calcium carbonate every hour in outpatients, but this antacid may have produced sufficient acid rebound so as not to have allowed adequate neutralization to permit healing of the gastric ulcers. In another controlled trial, Hollander and Harlan (229) showed that in patients with gastric ulcer treated with 420 mg calcium carbonate, two tablets hourly, pain relief and ulcer healing were significantly better than in the placebo-treated group. There was no significant healing effect in patients with duodenal ulcer by follow-up radiological studies.

Low-dose (287) and intensive regimens of potent antacids are equivalent to cimetidine in the healing of duodenal (151,242,408) but not of gastric ulcers (244,479). For example, Ippoliti et al (242) reported that in the 60 DU patients treated with cimetidine, 1200 mg daily, and in the 69 DU patients treated with Mylanta® II, 7 oz daily, the cumulative percent healed on antacid at 2, 4 and 6 weeks was 33%, 64% and 80%; on cimetidine, healing at these times was 25%, 62% and 86%. Combining the results of the four studies, the four and six week healing rates for cimetidine were 65% and 84% respectively, and for antacid were 63% and 72% respectively. Symptom relief was comparable in both treatment groups. Interestingly, Sturdevant et al (512) showed that antacids were no better than placebo for pain relief in hospitalized patients with DU. A dissociation between ulcer symptoms and healing by endoscopic criteria was also noted by Peterson et al (408).

Poor compliance may be a problem with antacid therapy (452), although we have observed that under the encouragement and watchful eye of a research nurse, patients consumed close to their prescribed antacid intake over a six week interval (479).

F. Liquid Versus Tablet Preparation

Although antacid tablets are convenient, liquid preparations are considered to be more effective because their buffering capacity is superior to that of tablets. For this reason, liquid antacids have been preferred.

Choice and use of Antacid

Antacids vary widely in their in vitro H^+ neutralizing capacity, in their sodium content, in their cost, and in their flavor. Select one of the new potent Mg-Al containing antacids such as Maalox Plus or Mylanta II, and switch from one to another, depending upon the patient's taste preference. While some clinical studies have suggested that a high dose antacid regime does heal duodenal ulcers, these same studies suggest that antacid is no better than placebo for the relief of symptoms. Amazing that generations of North Americans from Canada to Mexico have used antacids for the relief of acid indigestion, now only to be told that this was all a placebo effect! Clearly the results of carefullly conducted and controlled clinical trials may not apply to everyone's experience in practice. Compliance to a high-dose antacid regime is necessary to achieve ulcer healing, but many patients will not take all the recommended dose, even when under the watchful eye of the nursing staff of a Veteran's Administration Hospital (446). Most patients consider that antacids relieve their dyspeptic symptoms, and the patient will eagerly agree to consume sufficient antacid in order to achieve that relief. Remind yourself and your patient that the antacid liquid is much more potent than the tablets (59).

In summary, the recent resurgence of interest in antacids has confirmed the usefulness of aluminum-magnesium combinations of these pharmacological agents in the healing of duodenal and gastric ulcers. Therapeutic doses of antacids given with meals buffer the gastric acidity for prolonged periods and lower the intragastric pH to levels even below that observed with H_2-receptor antagonists. The modern potent antacids are well tolerated by patients. However, the antacids have no obvious advantage over the H_2-receptor antagonists for the healing of acute duodenal or gastric ulcers. Perhaps they may usefully play a role for the relief of recurrent mild symptoms which occur from time to time in the patient with known chronic ulcer disease. Certainly for the treatment of acute ulcers, antacids have been largely replaced by the H_2-blockers and by sucralfate. Some patients who take antacids on an as-required basis for pain may find that they require increasingly large doses of antacids for pain relief. Often the physician will see the patient when large doses of antacids have already been self-prescribed by the patient, and have been found to be inadequate to control symptoms. Clearly, under these circumstances, the patient requires more potent modern-day therapy. Should the antacids be continued with the H_2-blocker? Since there is evidence that at least one antacid reduces the absorption of oral cimetidine given simultaneously (508), these two agents should not be given together. When cimetidine is followed 1 and 3 hours later by Mylanta, the blood levels of cimetidine are unaffected (328).

Is there any evidence that the combination of antacid plus cimetidine is beneficial? Seven-times-a-day and four-times-a-day Mylanta II is effective in reducing intragastric acidity (328). Indeed, the larger dose of antacid is nearly as effective as cimetidine in reducing intragastric pH after meals and overnight. When cimetidine 600 mg with breakfast and at bedtime is supplemented with 30 cc Mylanta II one and three hours after lunch and after supper, even greater acid inhibition is achieved. It remains unproven, however, whether this combination of antacid plus cimetidine accelerates healing more than with cimetidine alone.

NEWER AGENTS IN THE TREATMENT OF ULCER DISEASE

PROSTAGLANDINS

Prostaglandins are lipid hormones found in nearly every body tissue. They have profound and diverse physiological and pharmacological effects which depend on the class of prostaglandin and on the target tissue. Some prostaglandins inhibit acid secretion, possibly by gastric mucosal adrenyl cyclase (441,529). Certain prostaglandins have been shown to protect the gastric mucosa against necrotizing agents such as absolute ethanol, 0.6 M HCl, 0.2M NaOH, hypertonic NaCl, and boiling water (439). This property of prostaglandins has been called "cytoprotection", and may be due to several mechanisms (Table 14).

TABLE 14. EFFECT OF PROSTAGLANDINS ON GASTRIC MUCOSA

1. Inhibit acid secretion

2. Increase mucosal blood flow

3. Increase gastric bicarbonate secretion

4. Increase thickness of unstirred layer gel mucus

5. Increase alkaline microclimate

6. Increase active chloride transport

7. Reduce gastrin response to food

Both natural and synthetic analogue E prostaglandins have been shown to decrease basal, pentagastrin-stimulated and histamine-stimulated gastric acid secretion in man (441). The E prostaglandins probably exert this anti-secretory effect by preventing histamine from stimulating the formation of its requisite mediator, cyclic AMP, by parietal cells. Some synthetic PGs may also have an antigastrin effect (330).

Vagally-stimulated gastric acid secretion is usually smaller than that occurring during maximal stimulation with gastrin. A staple prostaglandin E_2 analog (15-R-15 methyl PGE_2) given orally significantly reduced gastric acid and pepsin secretion in response to modified sham-feeding (MSF) in eight patients with chronic duodenal ulcer disease (274,275); serum concentrations of pancreatic polypeptic were suppressed in response to MSF, but the gastrin response was unaffected. Suppression of prostaglandin generation in the gastric mucosa with aspirin did not influence the secretory or hormonal responses to MSF. This suggests that exogenous but not endogenous prostaglandins are effective inhibitors of this vagally-induced gastric secretion.

Both natural and synthetic prostaglandins (PGs) are potent anti-ulcer agents, and are capable of preventing gastric mucosal injury (437,439-441) as a result of their anti-secretory and "cytoprotective" properties (95,96). PGs stimulate alkaline secretion and thereby alkalinize the microclimate adjacent to the membrane (181,260,263,365).

The gastric mucosa may protect itself against acid peptic digestion by maintaining an alkaline zone in the mucus layer coating its surface (17,52,430,445,518,555). The alkaline environment in this "mucus-bicarbonate" barrier, present when the luminal contents are acid, is enhanced in rats given 16-16-dimethyl prostaglandin E_2 (176,261,365,445).

Gastric mucosa is present in two forms, one solubilized in gastric juice and the other adherent to the surface epithelium. The amount of soluble mucus in gastric juice is increased by certain prostaglandins (66,255,395), and perhaps a change in the composition of one or both of these mucus components is more important than the thickness of the adherent mucus in the production of cytoprotection (7,66,176,263,438). When mild irritants are administered even only a few moments before necrotizing agents, mucosal necrosis is prevented, a process known as "adaptive cytoprotection" (96,440). If the production of endogenous prostaglandins is blocked with indomethacin, a cyclooxygenase inhibitor, then adaptive cytoprotection is also blocked (95,440). Robert et al (438) have recently challenged the idea that gastric cytoprotection is due to a change in the thickness of the gastric mucosa layer, as measured with a pachymeter. This lack of effect of 16, 16-dimethyl PGE_2 on mucus gel thickness is contrary to a previous finding (52).

In healthy subjects, mucosal prostaglandin generation in the duodenum is induced post-cibum in relation to duodenal acid load (3). This may be a physiologic example of adaptive cytoprotection. In patients with duodenal ulcer disease, prostaglandin synthesis activities in mucosal biopsy specimens taken endoscopically from the duodenal bulb before and after a meal changed little or decreased. Perhaps in duodenal ulcer disease there is a defect in the food-related change in mucosal PG synthesis occurring as a result of enhanced duodenal acid loads.

Misoprostil (SC-29333, Searle) is a synthetic analog of prostaglandin E, which has been shown in animals to reduce gastric secretion of acid and to be cytoprotective (109,116,117). Hunt et al (232) have demonstrated in 12 healthy subjects that 50 mcg misoprostil reduces gastric bleeding and secretion occurring in association with the ingestion of aspirin (975 mg four times a day). The reduction of bleeding was directly correlated with the reduction in acid. In the dog, the cytoprotective effect against aspirin is believed to be in part a consequence of an increased gastric mucosal flow (296).

A recent multi-center, double-blind, placebo-controlled study has shown that misoprostil (Searle), 200 mcg given four times daily, is highly effective in healing duodenal ulcers after four weeks of treatment (73). The degree of efficacy of misoprostil at four weeks (80% of patients had complete ulcer healing) is comparable to that reported for high-dose antacids, ranitidine, and sucralfate, and somewhat greater than that reported in some series for cimetidine and for another synthetic analogue of prostaglandin E_2 (543). Also, in a multi-center study with over 110 patients with active duodenal ulcer disease, enprostil, a synthetic dehydroprostaglandin, taken twice daily by mouth, was highly effective in the two- and four-week healing rates (Thomson et al, unpublished observations, 1984). Side effects were mild. This potent ulcer healing effect was likely achieved by the anti-secretory and anti-gastrin properties of this compound (330). In addition, the 15, 15-dimethyl analogues of PGE_2 has been shown to be effective in the healing of duodenal ulcer (181,460,461).

As yet there is no data on the rate of recurrent ulceration following prostaglandin-induced healing, nor is there data on the use of prostaglandins to maintain ulcer healing. As yet there is no support for the use of prostaglandins in the healing of gastric ulcers (461). Patients treated with synthetic prostaglandins may have diarrhea, but this is usually mild.

BISMUTH

Denol®, tripotassium di-citrato bismuthate (TDB), is a colloidal bismuth preparation which is effective in ulcer healing. It chelates with protein at an acid pH contributing to its anti-peptic activity (21,465). It may also stimulate mucus release (249). The pH and bacterial flora of gastric aspirate did not change during TDB therapy (204). In four to six weeks the healing of duodenal ulcers is approximately 80% with TDB and 25% for placebo (112,123,249,299,300, 374,465,480,481,542). Thus the efficacy of TDB is comparable with cimetidine for the healing of duodenal ulcers (481,542). On follow-up, endoscopically-proven relapse of DU occurred within one year in 47% of TDB-healed ulcers in comparison with 60% of cimetidine-healed ulcers. Bismuth-induced duodenal ulcer healing may be more sustained than cimetidine-induced healing (344).

The mean four- to six-week healing rates for gastric ulcers were approximately 85% with TDB and 33% with placebo (72,300,375,515). Bismuth is also comparable with cimetidine for the healing of gastric ulcer (295,520,552).

While liquid TDB has been proven to be effective in the healing of peptic ulcer disease, the development of a tablet form is welcomed. The tablet form is effective in ulcer healing and in pain relief (203,204,542).

Because serum and urinary bismuth levels rose during the six week treatment with TDB, and urinary excretion remained elevated two weeks after cessation of therapy, the possibility of the development of neurotoxicity cannot be ignored (6). However, there have been no reported symptoms or signs of adverse CNS effects suggestive of bismuth toxicity in patients taking TDB. The stools may blacken, the tongue may darken, and the compound may smell and taste poorly, especially when formulated as a liquid. Milk and antacids may interfere with the action of TDB and should be avoided one hour before and after taking TDB.

TDB is not currently available in the United States of America.

TRIMIPRAMINE

Trimipramine (Surmontil®), a tricyclic anti-depressant, increased the healing rate of DU (382). Confirmation of this finding is required. Sedation and mouth dryness may occur. Trimipramine is also not currently available in U.S.A.

CARBENOXOLONE

Carbenoxolone is synthesized from glycyrrhizic acid extracted from licorice root (483,484). It increases the life span of gastric epithelial cells (140,312), alters the carbohydrate composition of gastric mucus (139,484), increases the thickness of gastric gel mucus (56), has a variable effect on the gastric mucosal permeability to hydrogen ions (119,483) and inhibits peptic activity in gastric juice (45). Carbenoxolone has no influence on the secretion of gastric juice (34).

Clinical trials have reported the benefit of carbenoxolone sodium (Biogastrone®) in the treatment of GU (39,179,411,475,538) with mean 6 - 12 week healing rates of 65% with carbenoxolone and 37% with placebo. However, efficacy is not universally the case (179,359,475,556). The healing rate of gastric ulcers with cimetidine may be superior to healing with carbenoxolone (282).

In double-blind, endoscopically-controlled studies conducted over a 6 to 12 week period in patients with duodenal ulcer, the mean healing rate in patients treated with a position-release carbenoxolone capsule (Duogastrone®) was 68%, compared to 32% for placebo therapy (1,10,120,390,484,561). Symptom relief is satisfactory, but therapy may need to be continued for up to three months, and overall the evidence for the efficacy of carbenoxolone in the healing of DU is not considered to be strong (234).

It must be cautioned that at least one quarter of patients treated with carbenoxolone have a significant side effect, such as hypertension, weight gain, edema, and hypokalemia (81,119,120,135,190,194,297,427).

Bismuth, carbenoxolone and trimipramine are not currently available in the United States. In Canada, carbenoxolone has not gained wide acceptance because of its potentially serious side-effects. Trimipramine is used occasionally in patients with relatively intractable disease in whom there may be an element of associated depression. Bismuth is available in Europe, but its use is limited by the lack of palatability, althought the tablet form may overcome this problem.

OMEPRAZOLE

Benzimidazole derivatives such as omiprozole represent a new class of drugs which probably inhibit gastric H^+ secretion by suppressing the activity of H^+/K^+-ATPase, an enzyme playing a key role in the proton pump of parietal cells (153-155,399,400,485). Studies in animals have shown that these agents inhibit acid secretion induced by a variety of stimulants in vivo and in vitro (153-155,399,400,485). Olbe et al (400) reported a dose-dependent reduction in pentagastrin-stimulated H^+ secretion with one of these agents in healthy volunteers. The reduction lasted over 36 hrs after a single oral dose of the drug. In patients with chronic duodenal ulcer disease, two and six µmol/kg of omeprazole were associated with 50% and 90% reduction in acid outputs and acid concentration in response to modified sham feeding and pentagastrin, without affecting serum gastrin and pancreatic polypeptide response to modified sham feeding (273).

Omeprazole given intragastrically in both inhibitory and non-inhibitory doses to rats prevented dose dependently ASA- and ethanol-induced gastric lesions (272). The protective effect of omeprazole against ASA-induced lesions occurred when mucosal generation of PGs was completely suppressed (and that against ethanol lesions when PG generation was increased.) Thus inhibiting the H^+/K^+-ATPase involved in the final step of H^+ secretion protects the gastric mucosa against these two damaging agents by a mechanism unrelated to gastric inhibition of acid secretion or the biosynthesis of mucosal prostaglandins.

Unfortunately clinical trials with omeprazole were abruptly terminated when tumors developed in experimental animals given this compound.

PROGLUMIDE

DL-4-benzamide-N,N-dipropyl glutaramic acid, is a specific inhibitor of the effect of gastrin on the gastrin receptors present on parietal cells (99,452,453,553). It does not inhibit the secretory effects of histamine or acetyleldine (19,453). Proglumide inhibits the binding of gastrin to its receptor in rat oxyntic gland mucosa, and blocks the trophic action of exogenous gastrin in duodenal mucosa, colonic mucosa, and pancreas as well as oxyntic gland mucosa (256). Whereas cimetidine caused increases in serum gastrin levels and rat parietal cell volume, no changes were noted in rats treated with proglumide (544). In patients with the Zollinger-Ellison Syndrome (ZES), peptic ulcers are due to gastric acid hypersecretion which unambiguously results from hypergastrinemia. In three patients with

ZES, proglumide was much less potent than cimetidine, when compared on a molar basis, in inhibiting gastric acid secretion (291).

CHOLESTYRAMINE is of no proven benefit in the healing of GU (58).

AMYLOPECTIN SULFATE is a synthetic sulfated polysaccharide that inhibits pepsin secretion and forms a mucus-like layer of sulfate polysaccharide. Its therapeutic role in the treatment of DU is insecure. Deglycyrrhizinised liquorice (CAVED-S®) has been shown to be beneficial for the healing of GU and DU (524), but these results were not confirmed in two other reports (152,379).

SULPIRIDE

(N-(1-Ethyl-2-pyorrolidylmethyl)-2-methoxy-5-sulfamoylbenzamide), a neuroleptic drug which is a centrally acting antiemetic and analgesic, has been successfully used in the treatment of ulcers, but experience with the compound is limited.

OTHER H_2-RECEPTOR ANTAGONISTS

Oxmetidine is a new histamine H2-receptor antagonist with strong inhibitory effects on gastric secretion. It has several potential advantages over cimetidine, including low penetration of the central nervous system and absent antiandiogenic effects. Oxmetidine is comparable with cimetidine in the four- and eight-week healing of duodenal ulcers (319), but clinical trials in North America were abruptly discontinued when hepatotoxicity was reported.

YM-11170 is a new, clinically distinct H_2-receptor antagonist (516-518). Clinical trials are awaited.

UNRESOLVED ISSUES

1. Applicability of Clinical Trials.

Endoscopically-controlled prospective randomized trials extending from four to twelve weeks have shown that approximately 2/3 - 3/4 of patients with gastric or duodenal ulcers will heal on ranitidine, cimetidine, sucralfate or high-dose potent antacids. How applicable are the results of these controlled therapeutic trials to the goals which we set for our own patients? We need to apply our experience, common sense, and whatever other pieces of information or influence which appear to be appropriate. In the end, for your patient, and at a given point in time, you need to make a decision and to act, even in the face of legitimate differences in opinion based on interpretation of the data base, i.e. the clinical trials, and experience, i.e. the application of this new information to an individual patient. "My message is that results of controlled trials cannot be expected to define standard therapy. Rational therapeutic decision-making requires judgements about issues that cannot be settled with certainty by controlled trials" (511). Thus, the treatmemt for each patient must be individualized.

2. Hypersecretors.

The U.S. experience with cimetidine in Zollinger-Ellison Syndrome (ZES) has been renewed (351,353). This topic is discussed elsewhere in this book. Of interest though is the observation that some patients require high doses of cimetidine to obtain symptomatic relief, while other patients are never adequately controlled (67,68,113,128,360-362). This occasional poor response to cimetidine may be due to a diminished oral bioavailability and to a decreased pharmacologic response to the drug (563). In ZES patients, there is a positive correlation between the outcome of treatment and the reduction of gastric acidity, as measured by 24 hr pH profiles. Ranitidine is a more potent antisecretory agent, and either alone or in combination with an anticholinergic may be more effective than cimetidine in reducing gastric acidity (322,361,540). A large variable in the pharmacokinetics of orally-administered cimetidine has also been noted in non-ZES patients with duodenal ulcer disease (331). While some ZES patients failing on cimetidine will be better controlled on ranitidine, it remains to be determined whether similar bioavailability or response problems will plague the newer H_2-receptor antagonists. Not all DU patients are hypersecretors, but in those who are, it is unclear whether the dose of medication needs to be tailored to their acid output.

3. Endoscopy versus barium meal.

Barium meal is still the most commonly requested investigation in those patients suspected of having a peptic ulcer. The false-negative rate of upper GI series is about 20%, and posterior wall gastric ulcers and those in the second part of the duodenum are the most frequently missed. Also, if the duodenal cap is scarred, it may be difficult to differentiate between inactive and active disease. If the barium meal shows a DU, endoscopy is usually not necessary. Although an experienced radiologist can usually distinguish GU from cancer, it is now common practice to use endoscopy and biopsy in all patients with gastric lesions. However, can we be dogmatic? Should all patients with a gastric ulcer have endoscopy? This is indeed a controversial issue. The patient who presents with dyspepsia may well be initially treated with antacids, and undergo an upper GI series only if the symptoms persist. If the gastric ulcer appears to be benign, using numerous well-accepted radiological criteria (314), then under most usual circumstances it would be acceptable to heal the patient's ulcer with sucralfate or with H_2 blockers, and to repeat the upper GI series in six weeks. If the ulcer has not healed at that time, or if there is any question whatsoever, based on the clinical scenario or the radiological findings, that the lesion may be possibly malignant, then endoscopy should be obtained in order that multiple biopsies may be obtained. My own preference however has been to perform endoscopy on all patients with a radiologically demonstrated GU.

Early gastric cancer is common in Japan, and studies from that country have indicated that some reduction in the size of these lesions may occur with anti-ulcer treatment in three-quarters of patients (464). However, complete healing may be relatively uncommon (15). If the patient with persistent dyspepsia has a negative upper GI series, then endoscopy is indicated, as part of the diagnostic work-up. If a gastric ulcer is identified, then the endoscopy should be repeated after six weeks of treatment. If the ulcer was seen on upper GI series, was followed to radiological healing, but then recurs within several months, then it would be prudent to reassess, this time by endoscopy rather than by x-ray.

4. FOLLOW-UP

Gastric ulcers heal at an approximately fixed rate, so that it takes longer for large than for small ulcers to heal. Thus it may be necessary to continue to treat the patient with a large gastric ulcer for longer than the usual six weeks. After healing of a gastric ulcer, what follow-up is appropriate? If symptoms recur, the patient should have endoscopy, even if the initially-identified lesion was seen radiologically and was followed to healing on upper GI series. This suggestion for endoscopy rests on the concern that the x-ray which allegedly showed healing may have been in error. Furthermore, the recurrent ulcer should not, under these circumstances, be considered automatically to be benign.

5. ULCER AFTER SURGERY

Stomal or post-operative ulcer is defined as an ulcer in the stomach, duodenum, or jejunum of patients previously subjected to surgery for ulcer disease. The yardstick by which surgical results must be measured is the massive review experience of Stabile and Passaro (504). The conventional medical treatment of these ulcers is unsatisfactory, with an ulcer persistence rate of 42% and an ulcer-related mortality of 11%. Several previous controlled and uncontrolled reports have supported the benefit of cimetidine on healing or symptoms of perianastomatic ulcer after gastric surgery (46,100,125,150,157,199,215,227,265,266,286,415,470,506,531,549)

6. TREATMENT FAILURES: RECURRENT ULCERS OR RECURRENT SYMPTOMS?

Why does about one patient in five fail to heal after an acceptable course of an acceptable H_2 blocker? Is there excessive vagal tone, resulting in excess acid secretion? Or, more likely, is peptic ulcer disease such a multifactorial polymorphous condition that turning off the acid secretion is ineffective, because acid hypersecretion had little to do with the pathogenesis of the ulcer in the first place? These questions have not yet been answered, but many patients who do not heal on one anti-ulcer agent will heal when switched to a second drug, or when two drugs are combined. Such combination therapy includes H_2 blockers plus antacids or H_2 blockers plus anticholinergics. Alternatively, healing of resistant ulcers may be achieved when sucralfate is substituted for an H_2-receptor antagonist.

7. COMBINATION THERAPY

Potentiating interactions between the three receptors have a theoretical basis, and have been shown with isolated canine cells: there are potentiating interactions between histamine and gastrin and between histamine and carbachol, but not between carbachol and gastrin (492,493). Clinically, the experience also supports an interaction between H_2 blockers and anticholinergics (329). Let us consider the interactions of antacids and cimetidine, and of anticholinergics and cimetidine. Gastric acidity (mEq/l) is reduced when one dose of antacid is given one hour after a meal, or when one dose of anticholinergic is taken one hour before a meal.* The combination of both medications was more effective in reducing acid secretion than when either agent was taken alone. When cimetidine is taken with pirenzepine, there is a greater reduction in nocturnal acidity, volume, and acid secretion (329). Others have also shown that metiamide plus propantheline bromide

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(Fordtran, unpublished observations, quoted in Peterson & Fordtran, Chapter 52, pg 891-913).

(25).

STRATEGIES FOR LONG-TERM ULCER TREATMENT

Only a minority of patients suffer from one of the complications of duodenal ulceration, hemorrhage, perforation or pyloric stenosis. The majority of patients are troubled only by ulcer pain. The main treatment objective for the management of a patient with a duodenal ulcer must be the relief of symptoms and ulcer healing. Symptoms may be relieved without ulcer healing, but ulcer healing must be accomplished in order to prevent the development of the ulcer-related complications.

There are three main strategies for ulcer treatment:

1. on demand treatment of ulcer symptoms, without regard to a duration of therapy likely to achieve ulcer healing;
2. intermittent treatment of acute episodes with a full course of therapy, even after symptoms have subsided;
3. maintenance treatment after acute ulcer healing with the full dose treatment.

The first approach is generally viewed as being unsatisfactory, since ulcer healing is not necessarily achieved. The second approach is acceptable only if the patient has mild non-recurrent or infrequently recurring disease. The best results are obtained with the third strategy, using maintenance therapy. The disadvantages of chronic exposure to any drug are adverse reactions, cost, and lack of compliance leading to lack of efficacy. For the patient with difficult duodenal ulceration, these disadvantages are minor, compared with the potential hazards of elective or emergency surgery. At present, none of the medications proven to be useful for the treatment or maintenance of patients with ulcer disease change the natural history, or cure the disease.

Should H_2-blockers or sucralfate be taken "forever and ever"? Carefully controlled clinical trials address the question of the efficacy of these agents in the prevention of ulcer recurrence, but does such an approach represent sound judgement and common sense? The patients entered into clinical trials are highly selected and may not necessarily reflect the type of patient generally seen in practice. Many practitioners treat dyspeptic symptoms without endoscopy or x-ray evidence of ulcer. Many of these patients will enjoy an improvement in their symptoms. Probably no more than half of these patients have an ulcer, and many of those patients with non-ulcer dyspepsia who improve on ulcer therapy will have non-ulcer dyspepsia, or what Dr. Howard Spiro calls "Moynihan's disease" (502). These patients are not subject to the risk of complications of ulcer disease, and should not be placed on maintenance therapy. In the patients with a proven ulcer, perhaps we should wait for a recurrence, before placing them on maintenance therapy. This essence of time will allow for the selection of those peptic ulcer patients who will be "bad actors" and will have recurrent and therefore potentially more serious disease. Then, "once an ulcer, always an ulcer". However, future recurrences may be of ulcer-like dyspepsia without ulceration. If a recurrence of ulcer is proven, then maintenance therapy may be used. In this way the relatively low risk of complications can be weighed against the equally low risk of H_2-blocker related side effects.

After the six to eight course of therapy for the acute event, how should the therapy stop? While there is no evidence of "acid rebound" under these circumstances, many seasoned clinicians' practice is to gradually reduce the dosage of therapy over an interval of several weeks, down to the maintenance dose. For cimetidine, taken four times a day, this reducing regime would be the withdrawal of first the lunchtime, then the suppertime dose, then the breakfast dose. A decision is then made whether the patient is suitable for maintenance therapy. For ranitidine, the situation is even simpler: if the patient is receivng 150 mg. b.i.d., then the morning dose is stopped after the six to eight week therapeutic course. If the patient were taking ranitidine 300 mg at night during the period of active treatment, then she/he simply reduces the dose from two to one tablet at bedtime. If the patient who suffers a symptomatic recurrence over the following months, another course of H_2 blocker in the usual acute therapy dose should be given. If the patient had not been on maintenance therapy previously, then this therapeutic decision should be made.

An ulcer may recur with or without symptoms, and equally well, a recurrence of symptoms does not necessarily mean recurrence of the ulcer. Thus maintenance therapy may continue the healing of the ulcer, yet the pain returns. Alternatively the pain may subside while the ulcer recurs or persists. What then is the best approach to the patient with recurrent symptoms while on maintenance therapy? There are no studies on this point, but it makes considerable sense to increase the dose of ranitidine or cimetidne to the full therapeutic dose, from the maintenance dose. If the pain persists, the patient should undergo repeat endoscopy. If the pain or ulcer are show to disappear on the reinstituted full dose regime, then switch from one to another H_2 blocker, or switch to an agent that works by a separate mechanism, such as sucralfate.

Just as there are wide differences in placebo healing rates, so also is there wide variation in the recurrence rates between different countries and even within countries: from approximately 16% in West Germany to 60% in Austria. Recurrence rates as high as 80% in one year have been reported for patients who healed on cimetidine and continued either on placebo or off cimetidine maintenance (27,28,63). This contrasts with an average annual recurrence rate of about 20% in patients maintained on cimetidine (47,159,225).

It is unlikely that cimetidine enhances the likelihood of an ulcer recurrence, since there was recently reported to be no difference in the frequency of recurrences in patients previously healed on cimetidine or on antacids when endoscopies were performed when the patients were symptomatic or at three, six and 12 months. For example, at 3, 6, and 12 months, the cumulative percentages of patients with recurrence were 20%, 56% and 70% for antacid, and 36%, 55% and 75% after cimetidine therapy (240). This protection against relapse appears to remain for as long as the drug is taken (51,207).

Gastric ulcers, like duodenal ulcers, tend to recur (314,413), and as long as the possibility of a malignancy has been excluded beyond a reasonable doubt, then maintenance therapy should be considered. However, the role of maintenance cimetidine in preventing gastric ulcer relapse is less clear. One study has shown no benefit over a six month period (281), three studies have shown a benefit of maintenance cimetidine over a 12 month period (57,326), but this benefit of cimetidine over placebo did not extend to 2 years (37).

A single dose of 400 mg of cimetidine at bedtime is as effective in preventing recurrences as 400 mg two to three times a day (29,47). However, maintenance therapy with cimetidine 800 mg nocte has been shown to have a lower relapse rate (65) than with the 400 mg dose (61). The ideal or necessary degree of acid inhibition is unknown, but the higher dose may be preferable (159).

Maintenance therapy with ranitidine (150 mg nightly), cimetidine (400 mg nightly), or antacids (as needed for symptomatic relief) was studied in patients whose duodenal ulcers had been healed with cimetidine, ranitidine, or pirenzeprine. After 12 months, no recurrence of ulcers was observed in 75% of 40 patients on ranitidine, 78% of 20 patients on cimetidine and 40% of 50 patients on antacids (74).

Pirenzepine is as effective as cimetidine in preventing duodenal ulcer relapses (173).

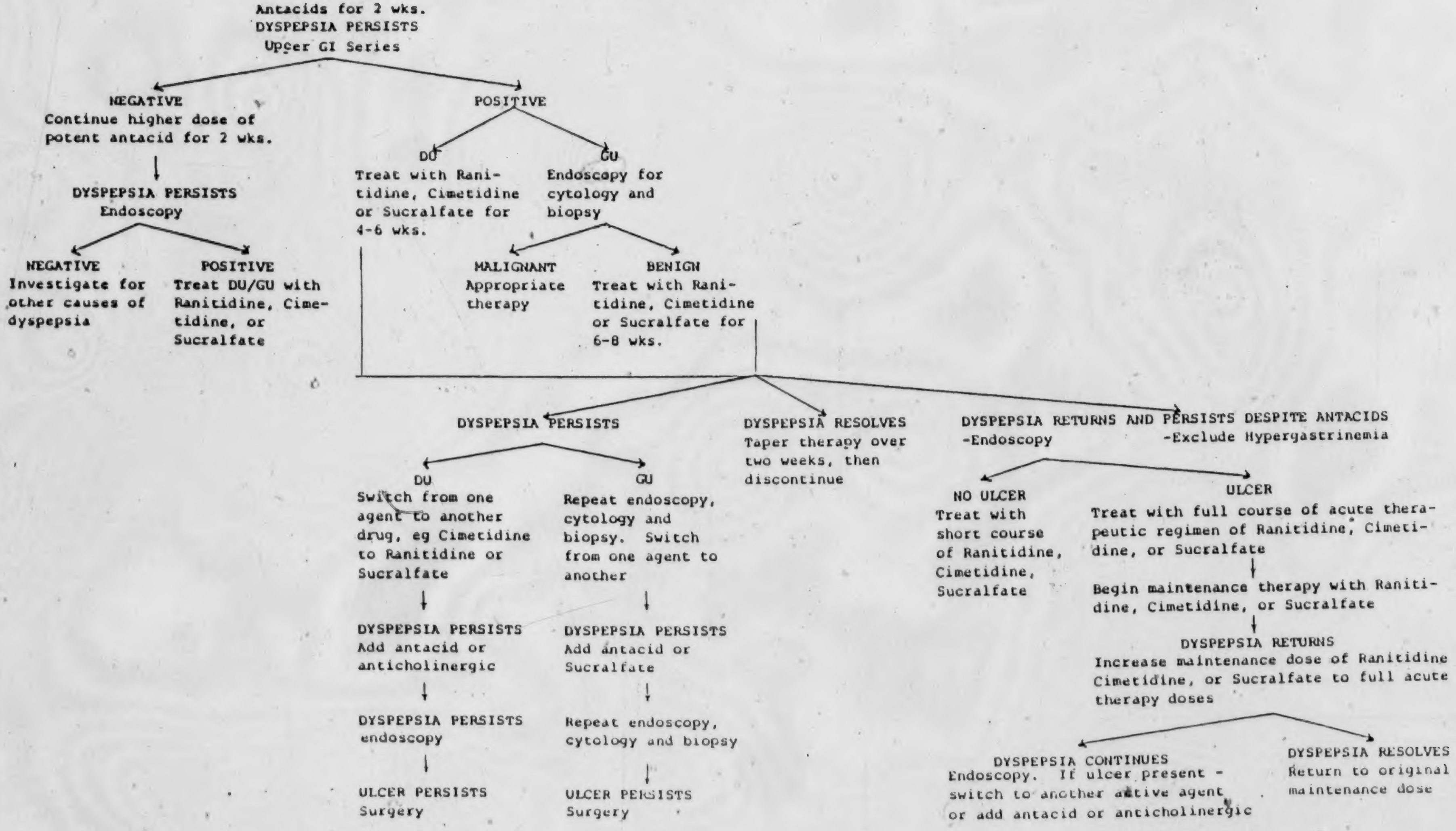
The results of an interim analysis of the ranitidine versus cimetidine multicentre study in the U.S.A. have recently been reported (482). A total of 125 patients with healed duodenal ulcers were randomly assigned to receive, nightly, either 150 mg ranitidine or 400 mg cimetidine. Endoscopic examinations were performed at baseline, and after four, eight and 12 months of therapy. Ulcer recurrence was assessed by the crude-rate method as well as by the more superior life-table method. By both methods the annual relapse rate was 2 1/2 times lower with ranitidine than with cimetidine. In a similar multicentre study from the United Kingdom, Eire and Australia, the relapse rate on ranitidine was about half that on cimetidine, when life-table analysis was performed at four, eight, and 12 months (186). Based on these data, it would appear that ranitidine is the superior H_2-blocker for maintenance therapy in peptic ulcer disease.

APPROACH TO THE PATIENT WITH ACID-PEPTIC DISEASE

While there are many causes of dyspepsia (528), acid pepsin disorders are likely among the most common. Many patients with dyspepsia will alter their diet or take non-prescription medications such as antacids, laxatives, or anti-gas agents in an effort to relieve their symptoms. It is uncommon then to see a patient with acid-pepsin symptoms who has not already, on their own accord, taken a bland diet and antacids, and avoided excessive dietary fat, spices, coffee. When these patients are seen for the first time for their dyspepsia, it is often sufficient for the family physician to place the patient on a full therapeutic regimen of antacids, and advise the patient to return for reassessment in two week's time (Table 15). If the dyspepsia persists, an upper GI series should be performed. If this is negative, or positive for gastric ulcer, endoscopy is required to attempt to identify an ulcer, which quite often may be missed on upper GI series, or to obtain cytology and biopsies from a gastric ulcer. If no ulcer is seen, further investigations need to be performed to establish the basis for the non-ulcer dyspepsia. If the gastric ulcer is benign, the patient should be treated for six to eight weeks with ranitidine (Zantac®, 150 mg., b.i.d. or 300 mg at night), or with cimetidine (Tagamet®, 300 mg., q.i.d. or 600 mg., b.i.d.) or with sucralfate (Sulcrate® 1 gm., q.i.d. one hour before meals and at night). Most patients will lose their symptoms of pain within several days, and must be reminded to continue their therapy for the full prescribed four to eight week course. It is

TABLE 15

APPROACH TO DYSPEPSIA


Antacids for 2 wks.
DYSPEPSIA PERSISTS
Upper GI Series
NEGATIVE
Continue higher dose of potent antacid for 2 wks.
DYSPEPSIA PERSISTS
Endoscopy
NEGATIVE
Investigate for other causes of dyspepsia
POSITIVE
Treat DU/GU with Ranitidine, Cimetidine, or Sucralfate
POSITIVE
DU
Treat with Ranitidine, Cimetidine or Sucralfate for 4-6 wks.
GU
Endoscopy for cytology and biopsy
MALIGNANT
Appropriate therapy
BENIGN
Treat with Ranitidine, Cimetidine or Sucralfate for 6-8 wks.
DYSPEPSIA PERSISTS
DU
Switch from one agent to another drug, eg Cimetidine to Ranitidine or Sucralfate
DYSPEPSIA PERSISTS
Add antacid or anticholinergic
DYSPEPSIA PERSISTS
endoscopy
ULCER PERSISTS
Surgery
GU
Repeat endoscopy, cytology and biopsy. Switch from one agent to another
DYSPEPSIA PERSISTS
Add antacid or Sucralfate
Repeat endoscopy, cytology and biopsy
ULCER PERSISTS
Surgery
DYSPEPSIA RESOLVES
Taper therapy over two weeks, then discontinue
DYSPEPSIA RETURNS AND PERSISTS DESPITE ANTACIDS
-Endoscopy
-Exclude Hypergastrinemia
NO ULCER
Treat with short course of Ranitidine, Cimetidine, Sucralfate
ULCER
Treat with full course of acute therapeutic regimen of Ranitidine, Cimetidine, or Sucralfate
Begin maintenance therapy with Ranitidine, Cimetidine, or Sucralfate
DYSPEPSIA RETURNS
Increase maintenance dose of Ranitidine Cimetidine, or Sucralfate to full acute therapy doses
DYSPEPSIA CONTINUES
Endoscopy. If ulcer present - switch to another active agent or add antacid or anticholinergic
DYSPEPSIA RESOLVES
Return to original maintenance dose

not necessary for the patient to continue to take their antacid while on one of these medications. However, many patients with chronic peptic disease habitually take antacids, and must be cautioned not to take their antacid within an hour of taking their cimetidine or sucralfate.

For the patient with a gastric ulcer, even if the patient is asymptomatic, endoscopy must be repeated in six to eight weeks to ascertain that the ulcer has healed. If the gastric ulcer persists, ensure that the patient has been taking their prescribed medication properly and for the full treatment period. If this is the case, then either continue therapy with the same agent for a further six to eight weeks, or switch to another drug, e.g. from cimetidine to ranitidine or from cimetidine to sucralfate. If on the third endoscopy the gastric ulcer is still unhealed, then surgery should be considered. If the gastric ulcer has healed, the drug therapy is gradually tapered over the next two weeks and is then discontinued. If the upper GI series demonstrated a duodenal ulcer, the patient does not require an endoscopy at that point and should be treated for four to six weeks with ranitidine, cimetidine or sucralfate. After the full therapeutic course, the drug therapy is gradually tapered, and then stopped.

Because some patients will have one episode of ulcer disease with no subsequent recurrences, maintenance therapy is not begun at this point. If the patient experienced a severe symptomatic recurrence, where he had previously had a duodenal or gastric ulcer proven on upper GI series or especially on endoscopy, then a further endoscopy is indicated. If the patient is found to have an ulcer, then he is treated with a full therapeutic regimen for the acute ulcer, and then placed on maintenance therapy with ranitidine (150 mg at night), cimetidine (300 mg, b.i.d. or 600 mg at night), or with sucralfate (1 gm at night). If the endoscopy shows that the symptomatic recurrence is not associated with a recurrence of ulcer ("non-ulcer dyspepsia"), then a full therapeutic course of H_2-blocker or sucralfate is used, but maintenance therapy is not indicated. Thus maintenance therapy is used only when it is "earned" by the radiological, or preferably by the endoscopic demonstration of the presence of an ulcer on two occasions (pain-ulcer-healing;-pain-ulcer-healing→maintenance).

If the patient develops pain while on maintenance therapy he may simply be experiencing a recurrence of non-ulcer dyspepsia, or a "breakthrough" ulcer. As long as there are no symptoms to suggest complications such as hemorrhage or gastric outlet obstruction, then endoscopy need not be performed and the dose of the maintenance medication is increased for four to eight weeks, then gradually tapered to the lower maintenance dose level. If breakthrough ulcers are occurring frequently, then consider switching the patient to another drug for maintenance therapy.

If during one of these episodes of pain the duodenal ulcer fails to heal after four to eight weeks of ranitidine, cimetidine or sucralfate, then several approaches may be taken to the treatment of these resistant ulcers. First, if the diagnosis of duodenal ulcer was made by upper GI series, then endoscopy becomes essential to confirm the diagnosis. If the ulcer is truly refractory to appropriate modern-day ulcer therapy, then switch to another drug. For example, cimetidine-resitant ulcers may heal on ranitidine. If the patient continues to have pain, or if the ulcer persists, then either add 7 times a day potent antacid (for example, Maalox Plus or Mylanta II, 30 one and three hour pc and at night) to the regimen of ranitidine, or add an anticholinergic to the regimen of H_2-receptor antagonist or sucralfate.

This approach to the patient with acid-peptic disease attempts to achieve the following goals (Table 16):

Table 16.

GOALS IN THE MANAGEMENT OF PATIENTS WITH PEPTIC ULCER DISEASE

1. the relief of symptoms,
2. the healing of the ulcer,
3. the maintenance of healing of the ulcer and the relief of symptoms,
4. the prevention of ulcer-related complications,
5. minimization of side effects of medical or surgical therapy, and the minimization of cost.

While some will consider this approach to be too conservative, others will claim that it is too aggressive. Nonetheless, it is a consensus approach, balancing the great efficacy of ranitidine, cimetidine or sucralfate, their excellent safety profile, and the high patient compliance, as compared with antacid. This approach also minimizes the requirement for overly frequent endoscopies, but recognizes that the prevention of recurrences and of complications are goals which must be evaluated with knowledge of the poor correlation between symptoms and activity of ulcer craters.

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CURRICULUM VITAE

NAME:	MAHACHAI, Varocha
BIRTHDATE:	October 13, 1951
PLACE OF BIRTH:	Bangkok, Thailand.
EDUCATION:	M.Sc. Program, Department of Medicine, University of Alberta, July 1982 - June 1984. Postgraduate Medical Training, July 1978 - June 1984, University of Alberta, Edmonton, Canada Postgraduate Medical Training, May 1976 - November 1977 Chulalongkorn University Hospital, Bangkok, Thailand M.D. (Second Class Honors), Chulalongkorn University, Bangkok, Thailand, 1972 - 1976. B.Sc. (First Class Honors), Chulalongkorn University, Bangkok, Thailand, 1970 - 1974. High School at Triam Udom College, Bangkok, Thailand, 1968-1969. Primary and secondary school at Matar Dei School, Bangkok, Thailand, 1957-1967.
POSTGRADUATE EXPERIENCE:	July 1982 - June 1984: Fellow in Gastroenterology, University of Alberta, Edmonton, Alberta, Canada. Enrolled in M.Sc. program funded by Alberta Heritage Foundation for Medical Research. July 1981 - June 1982: Third year resident, Internal Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada. (First 6 months in Gastroenterology). July 1980 - June 1981: Second year resident, Internal Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada. July 1979 - June 1980: Rotating Intern, University of Alberta Hospital, Edmonton, Alberta, Canada. July 1978 - June 1979: First year resident, Internal Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada. December 1977 - June 1978: Leave of Absence. May 1977 - Nov 1977: First year resident, Internal Medicine, Chulalongkorn University Hospital, Bangkok, Thailand. May 1976 - April 1977: Rotating Intern, Chulalongkorn University Hospital, Bangkok, Thailand.

PROFESSIONAL QUALIFICATIONS:	Fellow of The Royal College of Physicians and Surgeons in Internal Medicine (F.R.C.P.(C)), 1983. American Board of Internal Medicine, 1982. Examinations: ECFMG, VQE, FLEX (California), LMCC.
TEACHING EXPERIENCE:	Tutor in Gastroenterology for undergraduate medical students. Assist in teaching students and junior medical residents during their Gastroenterology rotation. Senior resident in Internal Medicine on Clinical Teaching Unit during third year residency 1982.
SCHOLARSHIPS AND AWARDS:	Alberta Heritage Foundation for Medical Research Fellowship, July 1984 - June 1986, for Clinical Pharmacology training at the University of California, San Francisco, U.S.A. Canadian Association Gastroenterology Award for the paper entitled "Comparison of Cimetidine and Ranitidine on 24 hour Intragastric Acidity and Serum Gastrin Profile in Patients with Esophagitis" to be presented at the Royal College of Physicians and Surgeons of Canada Annual Meeting in Montreal, September 1984. Alberta Heritage Foundation for Medical Research Fellowship, July 1982 - June 1984. Scholarships granted by the Chulalongkorn University, Bangkok, Thailand, throughout the university education for outstanding academic performace. Medal from the Chulalongkorn University Medical School for being the overall top student, 1976. Various other awards for being top student; and individual awards for being top student in individual subjects (including Medicine and Surgery) throughout the university education.
PROFESSIONAL ASSOCIATIONS:	Member of Royal College of Physicians of Canada. Member of Alberta Medical Association. Member of American College of Physicians. Member of American Gastroenterology Association. Member of Thai Medical Association.
REVIEWS:	External reviewer, Canadian Journal of Physiology and Pharmacology, 1984.

RESEARCH: A series of clinical studies to compare different antisecretory agents on 24-hour intragastric acidity in peptic ulcer patients, with emphasis on gastric physiology in health and disease, pathophysiologic mechanisms and pharmacokinetics. Enrolled in M.Sc. program, Department of Medicine (supervisor A.B.R. Thomson).

A pharmacokinetic study on intestinal and hepatic drug metabolism and Clinical Pharmacology and Toxicology, to be commenced in July 1984, at the University of California, San Francisco.

SCHOLARLY ACTIVITIES:

A. Manuscripts

V. Mahachai, K. Walker, F. Jamali, H. Navert, D. Cook, A. Syme, A.B.R. Thomson. Comparative effects of two cimetidine regimens on 24-hour intragastric acidity in patients with asymptomatic duodenal ulcer. Clin Ther, 6:#3 (Vol 6), 1984.

V. Mahachai, K. Walker, A.B.R. Thomson. Comparison of cimetidine and ranitidine on 24-hour intragastric acidity and serum gastrin profile in patients with esophagitis. Submitted to Dig Dis Sci, 1984.

V. Mahachai, F. Jamali, A.B.R. Thomson. Comparison of combination of Mylanta II and cimetidine on 24-hour intragastric acidity in patients with asymptomatic duodenal ulcer disease. (To be submitted to Clinical Therapeutics), 1984.

V. Mahachai, F. Jamali, P. Reilly, A.B.R. Thomson. Comparative effects of pirenzepine and cimetidine on 24-hour gastric acidity in duodenal ulcer disease. (To be submitted to Journal of Clinical Investigation), 1984.

V. Mahachai, K. Walker, H. Sevelius, A.B.R. Thomson. Enprostil, a dehydro-prostaglandin E_2, has potent antisecretory and antigastrin properties in patients with duodenal ulcer disease. (To be submitted to Gastroenterology), 1984.

V. Mahachai, A.B.R. Thomson. Interrelationship between gastric acidity and concentration in patients with duodenal or gastric ulcer, and normal subjects. (To be submitted to Digestive Diseases and Sciences), 1984.

B. Abstracts

V. Mahachai, M. Grace, A. Symes, D. Cook, A.B.R. Thomson. Comparison of two cimetidine regimens on 24-hour intragastric acidity in patients with duodenal ulcer disease. Gastroenterology 82:1122, May 1982.

V. Mahachai, M. Grace, A. Symes, D. Cook, A.B.R. Thomson. Comparison of two cimetidine regimens as 24-hour intragastric acidity in patients with duodenal ulcer disease. Clin Res 31:20A, February 1983.

V. Mahachai, A.B.R. Thomson. Twice daily cimetidine: Pharmacokinetics, 24-hr intragastric pH and gastrin profile. Annals Roy Coll Phys Surg Canada, #4, 354, June 1983.

V. Mahachai, K. Walker, R. Sherbaniuk, and A.B.R. Thomson. Intragastric pH and serum gastrin profiles in gastroesophageal reflux disease. Am J Gastro 78:699, October 1983.

V. Mahachai, P. Reilly, A.B.R. Thomson. Effects of pirenzepine and cimetidine on 24-hour intragastric pH and gastrin profile in patients with duodenal ulcer disease. Clin Res 32, 27A, February 1984.

V. Mahachai, K. Walker, H. Sevelius, A.B.R. Thomson. Enprostil, a dehydro-prostaglandin E_2, has potent antisecretory and antigastrin properties in patients with duodenal ulcer disease. Gastroenterology 86:1171, May 1984.

V. Mahachai, F. Jamali, P. Reilly, A.B.R. Thomson. Combination of pirenzepine and cimetidine on gastric acidity and gastrin profile in patients with duodenal ulcer disease. Gastroenterology 86:1171 May 1984.

V. Mahachai, F. Jamali, P. Reilly, A.B.R. Thomson. Pharmacokinetics and effect of pirenzepine on gastric acid secretion in duodenal ulcer disease. Gastroenterology 86:1171 May 1984.

C. Presentations

V. Mahachai, M. Grace, A. Symes, D. Cook, A.B.R. Thomson. Comparison of two cimetidine regimens on 24-hour intragastric acidity in patients with duodenal ulcer disease. Presented at American Gastroenterological Associaton, Chicago, May 1982.

V. Mahachai, M. Grace, A. Symes, D. Cook, A.B.R. Thomson. Comparison of two cimetidine regimens on 24-hour intragastric acidity in patients with duodenal ulcer disease. Presented at American Federation of Clinical Research meeting in Carmel, February 1983.

V. Mahachai, A.B.R. Thomson. Twice daily cimetidine: pharmacokinetics, 24-hour intragastric pH and gastrin profile. Presented at the annual meeting of the Royal College of Physicians and Surgeons of Canada, Calgary, September 1983.

V. Mahachai, A.B.R. Thomson. Comparison of mylanta II and cimetidine on 24-hour intragastric acidity in patients with duodenal ulcer disease. Presented at the Clinical Society for Clinical Investigation annual meeting, Calgary, September 1983.

V. Mahachai, K. Walker, R. Sherbaniuk, A.B.R. Thomson. Intragastric pH and serum gastrin profiles in gastroesophageal reflux disease. Presented at the American College of Gastroenterology annual meeting, Los Angeles, October 1983.

V. Mahachai, F. Jamali, A.B.R. Thomson. 24-hour intragastric acidity and cimetidine pharmacokinetics during combination therapy of cimetidine and Mylanta II. Presented at the 3rd Annual Heritage Medical Resesearch Days, Calgary, November 1983.

V. Mahachai, K. Walker, R.W. Sherbaniuk, A.B.R. Thomson. Comparison of cimetidine and ranitidine on 24-hour intragastric acidity and serum gastrin profile in patients with gastroesophageal reflux disease. Presented at the 3rd Annual Heritage Medical Research Days, Calgary, November 1983.

F. Jamali, V. Mahachai, A.B.R. Thomson. 24-hour intragastric acidity, gastrin profile and cimetidine pharmacokinetics during twice daily cimetidine. Presented at the 3rd Annual Heritage Medical Research Days, Calgary, November 1983.

V. Mahachai, K. Walker, H. Sevelius, A.B.R. Thomson. Enprostil, a dehydro-prostaglandin E_2, has potent antisecretory and antigastrin properties in patients with duodenal ulcer disease. Presented at American Gastroenterological Association, New Orleans, May 1984.

V. Mahachai, F. Jamali, P. Reilly, A.B.R. Thomson. Combination of pirenzepine and cimetidine on gastric acidity and gastrin profile in patients with duodenal ulcer disease. Presented at American Gastroenterological Association. New Orleans, May 1984.